LESIONS OF THE NERVOUS SYSTEM ASSOCIATED WITH INTERNAL DISEASES

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ПОРАЖЕНИЕ НЕРВНОЙ СИСТЕМЫ
ПРИ ВНУТРЕННИХ БОЛЕЗНЯХ

PUBLISHER'S NOTE

This book is intended not only for neurologists and therapeutists; it is of interest to the general practitioner as well. The book covers the clinic, pathological anatomy and pathogenesis of nervous lesions in internal diseases. It also sheds light on questions relating to the treatment of these lesions. Special attention is devoted to neuropathological syndromes observed in diseases of the cardiovascular system, blood and haemopoietic organs, the lungs, liver and metabolic disorders.

The second, revised and supplemented edition of this book was published in the Soviet Union in 1960.

TO THE READER

The Foreign Languages Publishing House would be grateful for your comments on the content, translation and design of this book. We would also be pleased to receive any other suggestions you may wish to make.

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CONTENTS

	Page
Foreword	7
Chapter I. LESIONS OF THE NERVOUS SYSTEM ASSOCIATED WITH CARDIOVASCULAR DISEASES	
Congenital Diseases of the Heart and Main Blood Vessels	9
Rheumatic Endomyocarditis	17
Cerebral Rheumatism. Embolism of Cerebral Vessels. Chorea Minor	18
Acute and Subacute Septic Endocarditis	23
Mycotic Aneurysms of Cerebral Vessels. Cerebral Abscess and Purulent Meningitis. Meningo-Encephalitis	25
Stenocardia and the Zakharin-Head Zones	28
Myocardial Infarction	33
Shoulder-Hand Syndrome	39
Chronic Cardiac Insufficiency	41
Paroxysmal Tachycardia	42
Heart Block and the Morgagni-Adams-Stokes Syndrome	44
Aneurysm and Aortic Thrombosis	46
Hypertensive Disease	51
Nervous Symptoms in the Initial Phases of the Hypertensive Disease. Rise in Intracranial Pressure. Hypertensive Crisis and Acute Cerebral Oedema. Transitory and Minor Focal Lesions of the Cerebrum. Cerebral Haemorrhage	51
Thromboangiitis Obliterans	70
Periarteritis Nodosa	82
Temporal Arteritis	99
Acute Systemic Lupus Erythematosus	107

Takayusu Syndrome (Pulseless Disease, or Aortic Arch Syndrome) 110

Chapter II. LESIONS OF THE NERVOUS SYSTEM ASSOCIATED WITH DISEASES OF THE HAEMOPOIETIC ORGANS AND BLOOD 113

Pernicious Anaemia (Addison-Biermer Disease) . . . 113
Erythraemia (Polycythaemia) 125
Leukosis 130
Lymphogranulomatosis 141
Haemorrhagic Diathesis 150
Multiple Myeloma (Rustitsky's and Kahler's Disease) . . . 153
Sarcoidosis (Besnier-Boeck's and Schaumann's Disease) . . 155

Chapter III. NERVOUS LESIONS ASSOCIATED WITH PULMONARY DISEASES 161

Tuberculosis of the Lungs 161
Vegetative Syndromes. Tubercular Neuritis and Polyneuritis. Serous Meningitis and Other Non-Specific Reactions. Embolism of the Cerebral Vessels During Artificial Pneumothorax 161
Cancer of the Lungs 170
Metastasis in the Central Nervous System. Neuritis. Pancoast's Syndrome. Polyneuritis 170
Pneumonia 175
Meningitis and Meningism. Serous Meningitis. Focal Lesions of the Brain. Polyneuritis 175
Pulmonary Abscess 179
Pulmonary Emphysema 180

Chapter IV. NERVOUS LESIONS ASSOCIATED WITH DISEASES OF THE DIGESTIVE SYSTEM 183

The Ulcerous Disease 183
Polyneuritis Associated with Intestinal Diseases 185
Wernicke's Haemorrhagic Polioencephalitis 187

Chapter V. NERVOUS LESIONS IN DISEASES OF THE LIVER 189

Hepatolenticular Degeneration 193
Hepatic Coma 202
Meningeal Syndrome 206
Polyneuritis 207

Chapter VI. NERVOUS LESIONS ASSOCIATED WITH DISEASES OF THE KIDNEYS 209

Azotemic Uraemia 209
Eclamptic Uraemia 214
Paralysis in Renal Hyperkaliemia 217

Chapter VII. NERVOUS LESIONS ASSOCIATED WITH ENDOCRINE AND METABOLIC DISORDERS 218

Thyrotoxicosis 219
Hypothyrosis and Myxoedema 222
Parathyroid Hypofunction (Tetany) 223
Diabetes Mellitus 226
Hypoglycaemia and Hyperinsulinism 239
Addison's Disease 246
Acute Porphyria 247

FOREWORD

The narrow specialisation which is characteristic of medical practice today makes it difficult to recognise and diagnose many diseases. The doctor often confines his diagnosis to the sphere of his own speciality, with no regard for the adjoining regions, and that leads inevitably to diagnostic and therapeutic mistakes.

This applies most of all to internal diseases and neuropathology. Not all diseases are diseases of the nerves, but the nervous system is involved in the development of all disorders. Its involvement in the pathological process changes and aggravates the clinical picture. This book represents an attempt to fill up the gap in this region of borderline medicine. I am referring to nervous syndromes which complicate internal diseases and are brought on by these diseases.

The book is based on my own observations collected over a period of many years. I am aware that it does not cover the subject in full and that it has a number of shortcomings, but the hope that it may prove useful to both neurologists and therapeutists prompts me to publish it.

THE AUTHOR

Chapter I

LESIONS OF THE NERVOUS SYSTEM ASSOCIATED WITH CARDIOVASCULAR DISEASES

CONGENITAL DISEASES OF THE HEART AND MAIN BLOOD VESSELS

Lesions of the nervous system connected with congenital heart defects represent a new and inadequately explored branch of clinical neurology. Now that operations are often performed for the purpose of correcting congenital defects of the heart, complications of the nervous system have acquired not only academic interest, but practical importance as well. In post-mortem examinations Berthrong and Sabiston found cerebral lesions in 25 out of 135 cases in which operations were performed on congenital heart defects. According to data of the Pathological Department of Clinical City Hospital No. 4 of Moscow (prosector Y. L. Rappoport), in 1956 the post-mortem examination of 10 cases of persons who died after operations revealed 3 cases of cerebral lesions (in one case there was a large cyst of the cerebral hemisphere, in the second case—multiple patches of red softening in both hemispheres, and in the third case—a haemorrhage into the pial membranes). According to Abbott, in cases of Fallot's tetralogy 15 per cent of the patients die of cerebral lesions. That is slightly less than the percentage of deaths from cardiac insufficiency.

Ordinarily, paradoxical embolisms are the only cerebral complications described in cases of congenital heart

diseases. In reality, however, these complications are quite diverse.

Paradoxical embolisms are observed most often in cases of combined congenital cardiac defects (tetralogy of Fallot). In isolated congenital heart diseases, paradoxical embolism is encountered most often in cases of potency of the foramen ovale, rather than in the case of a ventricular defect. The cause of embolism in this case is the propulsion of blood, carrying an embolus from the right into the left heart through the open partition which normally separates the venous from arterial blood circulation. In approximately 50 per cent of the cases embolism is a result of thrombosis of the veins of the lower extremities, or in the haemorrhoidal veins.

Isolated cases of paradoxical embolism into the brain were observed after bone fractures, or after delivery. In 20 per cent of the cases foramen ovale was blocked by a thrombus which extended towards both auricles. The clinical picture of paradoxical embolism is the same as in cases of cerebral embolisms of other etiology. For example:

Patient M., age 22, a manual worker, had no complaints to make about her health in the past and did not apply to doctors. In August, 1957, when she was at work, there was a sudden onset of right-side aphasia and dextral hemiplegia, without a loss of consciousness. An ambulance delivered the patient to Hospital No. 1 for infectious diseases with the diagnosis of serous meningitis; from there she was transferred to the neurological department of City Hospital No. 4 with the diagnosis: congenital heart disease, embolism of the left mid. cerebral artery.

Status praesens: Colouring of the cutaneous and mucous membranes normal, oedema absent, nutrition satisfactory. Consciousness clear, motor aphasia and elements of sensorial aphasia. Very pronounced dextral haemiparesis with high tendon reflexes. Positive Babinski's and Bechterew's symptoms on the right side.

Boundaries of the heart normal. Marked systolic murmur in the fourth intercostal space, conveyed with decreasing force to the sternum and vessels, with irradiations into the back as well. Murmur in the region of the fourth intercostal space. Arterial blood pressure 110/70 mm Hg. Liver and spleen not palpable. Blood and urine normal. X-ray of lungs and heart normal. The only marked feature

in the cardiogram is the vertical position of the heart axis. According to the conclusion of therapeutists, there are no indications of a current process in the heart. Formol and histiocytic tests negative. Blood culture sterile.

Considering the above-said a conclusion may be drawn that the patient suffers from a congenital heart disease: patent interventricular, or interatrial walls. The nature of the defect may be defined only by means of angiocardiography.

Disturbances in the cerebral blood circulation with the formation of a patch of softening in the brain can develop not only as a result of paradoxical embolism. Compensatory polycythaemia developing in certain cases of congenital heart diseases is concomitant with heightened viscosity of the blood, deceleration of the blood flow in the brain which stimulates the development of thrombi in the cerebral vessels. Anoxaemia and the deceleration of the blood flow of cerebral vessels can also cause a thrombosis of cerebral veins and sinuses with subsequent haemorrhages into the brain.

Paradoxical embolisms receive much more attention in literature than cerebral abscesses which occur quite frequently, according to the information of some authors.

We refer to our own observation.

Patient L., age 22, was brought to the hospital in a state of unconsciousness on December 17, 1949. At the age of three months the patient was found to be suffering from a congenital heart disease, patent foramen ovale. Growth and development normal. Made no complaints to doctors about his heart. During the last three weeks began to complain of severe headaches which were attributed to excessive mental strain. On December 10, acute pain appeared in the region of the left temple, the temperature went up to 38°C. Disturbances of speech appeared on December 15. Two days later the patient lapsed into unconscious state.

Patient in a state of coma. Temperature 39° C. The skin of the face and mucous membranes slightly cyanotic. Pupils dilated, do not react to light. Extremities drop limply when raised. Tonic convulsions from time to time in the left extremities. Abdominal reflexes absent. Tendon reflexes on the left brisker than on the right. Babinski's and Oppenheim's signs on both sides. Rigidity of the occiput and bilateral Kernig's sign.

Heart dilated to the left. Intensified first sound and systolic murmur at the left edge of the sternum extending to other apertures, pulse rhythmic, rate 68 beats per minute. Arterial blood pressure 160/100 mm Hg.

Spinal fluid: pressure 500 mm, albumin 0.49‰, cytosis 432 (neutrophils 80%, lymphocytes 20%). Blood count: Leukocytes 20,800, juvenile cells 1%, band cells 7%, segmented cells 78%, lymphocytes 8%, monocytes 6%, sedimentation of erythrocytes 22 mm per hour. Urine: Albumin 0.9%, no other deviations from normal.

The patient died 18 hours after admission to the hospital.

Clinical diagnosis: Congenital heart disease (patent foramen ovale), purulent meningo-encephalitis.

Autopsy revealed an abscess in the left temporal lobe of the brain, perifocal oedema and softening of the brain substance. Acute meningo-encephalitis. Heart dilated, its weight 380 grams. Patent foramen ovale. Constriction of aortic isthmus. Acute hyperplasia of the spleen.

Microscopic examinations revealed a solid capsule composed of collagenic fibers around the abscess; it indicated that the abscess originated at least 4 weeks before the patient's death. It is to be assumed that the formation of the abscess coincided with the appearance of headaches. The marked development of the clinical picture of the disease a few days before the patient's death is explained by the rupture of the abscess into the subarachnoid space and the resulting development of purulent meningo-encephalitis.

The absence of any disturbances of the ear, of the accessory sinuses of the nose, or any other purulent diseases in this case which could have caused an abscess of the brain, impels us to classify the latter as the so-called cryptogenic abscesses. However, the combination of the cerebral abscess with a congenital heart disease cannot be considered an accidental coincidence. The absence of sources of a cerebral abscess in the case observed and the mentioned facts from literature about the frequency of cerebral abscesses in cases of congenital heart diseases leave no doubt as to the direct association of the abscess with the congenital patency of the foramen ovale.

The pathogenesis of abscesses of this kind has not been adequately explored to this day. Symptoms of subacute

bacterial endocarditis are very rare. Roger, Poursines and Roger attach basic importance to paradoxical embolism. In their opinion, an infective embolus penetrates into the brain from the peripheric or visceral veins through the patent foramina in the ventricles or atria. Nevertheless, symptoms of infection of the veins in the case of such abscesses are rare; that is why most authors (Sancetta, Zimmermann and others) believe that a cerebral infarction is infected owing to transient bacteraemia originating in cases of diseases of the teeth, tonsils, of the upper respiratory tract, etc. The pathogenic factors penetrate from the right heart into the left, in spite of the filtering function and phagocytic action of the pulmonary alveoles. Of great importance in this case is the penetration of venous blood into the arterial system. In some cases of stenosis of the pulmonary artery combined with open communication passage between the ventricles or atria of the heart Selzer found cerebral abscesses in three out of 19 patients, while not even one abscess was observed by the author in the absence of such a communicating passage. The hypothesis concerning the role of an earlier lesion of the brain in the form of an infarction caused by embolism is confirmed also by experimental data. An injection of microbes into the carotid artery will not evoke an abscess of the brain, but an abscess can develop if the injection is made after a traumatic injury of the skull and brain.

Knowledge of the possibility of the development of a cerebral abscess in the case of the existence of a communicating passage between the right and left ventricles is of great practical value, inasmuch as it affords the possibility for a timely diagnosis and for surgical aid. Cases of this kind with successful operations were described by Smolik, Blattner, Heys, Cohen, Bergman and Malis. During ten years Campbell observed 14 patients with an abscess of the brain associated with congenital heart diseases: five of them underwent successful operations. A description of a patient suffering of Fallot's tetralogy and operated in con-

nection with two abscesses of the brain was given by Lafan and his collaborators. A successful operation for an anastomosis between the subclavian and pulmonary arteries was performed six months later.

A nervous lesion of a different nature is observed in cases of congenital coarctation of the aorta. The result is that the lower part of the body receives blood through the intercostal arteries and the internal mammary arteries. Arterial blood pressure is below normal in the lower extremities while it is considerably above normal in the brachial arteries and the Willis' circle arteries.

A rise in arterial blood pressure in the upper part of the trunk produces headaches, giddiness and inclination to vomiting. Some patients complain of pain in the legs of the nature of intermittent claudication. According to I. Littmann and R. Fono, 25 per cent of the adults suffering from coarctation of the aorta die of cerebral haemorrhages. In some cases these haemorrhages are caused by arterial hypertension in the Willis' circle, in other cases—by a ruptured aneurysm of Willis' circle vessels. Eppinger described in 1888 a coarctation of the aorta combined with a ruptured aneurysm of a vessel at the base of the cerebrum. Identical observations were published later by Woltman and Shelden, Weber, Baker and Shelden, and other scientists.

Here are some of our own observations.

Patient C., age 23, had not applied for treatment in the past; exempted from military service owing to a heart disease. On December 10, 1950, was suddenly overcome by an acute headache with vomiting and cramps in the arms and legs. Soon the patient lost consciousness and on the same day he was brought to the hospital.

Status praesens: State of coma. Occipital rigidity. Kernig's and Brudzinski's signs highly pronounced. Pupils dilated, do not react to light. Raised extremities drop limply. Tonic convulsions in the left extremities from time to time. Muscular tone of the extremities high. Tendon and abdominal reflexes absent. Babinski's sign on both sides.

Heart boundaries dilated to the left. Heart sounds dull. A sharp systolic murmur heard everywhere in the region of the sternum. Dilated, pulsating vessels visible on the back, between the scapulae. Arterial blood pressure 190/100 mm Hg. Pulse rhythmic, 100 beats per minute. Patient died 15 hours after admission to the hospital.

Clinical diagnosis. Ruptured aneurysm of a vessel at the base of the brain, subarachnoid haemorrhage.

Autopsy revealed a subarachnoid haemorrhage spreading mainly in the region of the base of the left cerebral hemisphere. A ruptured aneurysm 0.5 cm in diameter in the left anterior cerebral artery, at the point of diversion of the anterior communicating artery. The haemorrhage from the latter destroyed a considerable part of the left frontal lobe. Blood penetrated through the anterior horn into the cerebral ventricles which were filled up with blood clots.

Heart weight 340 grams, considerable hypertrophy of the wall of the left ventricle. Aorta severely contracted at the point of diversion of the subclavicular artery. A funnel-shaped constriction, its diameter barely reaching 5 mm, evident at the opening of the aorta.

In January 1957, we chanced to observe a similar case *ex concilio.*

Patient, 18 years of age, made no complaints in the past. High arterial blood pressure found during a screening in school in 1956. Headache, vomiting with subsequent loss of consciousness were brought on suddenly at the beginning of January after a physical exertion.

At the time of the examination the patient was in a state of coma. Pupils dilated, did not react to light. Sharp rigidity of the occiput, Kernig's and Brudzinski's signs. Lumbar puncture revealed haemorrhagic fluid. The patient did not regain consciousness and died five days later.

The autopsy revealed a severe coarctation of the aortic isthmus and a ruptured aneurysm of the anterior cerebral artery, the haemorrhage penetrating into the pial membranes and cerebral ventricles.

In the two mentioned cases, the patients suffering from aortal coarctation died of blood effusion into the brain due to ruptured aneurysm of a Willis' circle vessel. As already mentioned, this cause of death in cases of coarctation of the aorta was described about 80 years ago. Abbott found in literature 200 cases of coarctation of the aorta. In 18 of these cases death resulted from a haemorrhage into the brain from a ruptured aneurysm. According to Berthrong

and Sabiston, four out of 10 patients with coarctation of the aorta had an aneurysm of a vessel in a Willis' circle; in three cases death was caused by a subarachnoid haemorrhage. S. A. Chugunov and E. V. Golbert described a patient suffering of stenosis of the aortic isthmus; it was found that the patient had an aneurysm of the anterior spinal artery which caused repeated haemorrhages into the spinal cord. Wright described ten cases of ruptured aneurysm of vessels at the base of the brain in case of congenital coarctation of the aortic isthmus and described one of his own observations. An unruptured aneurysm was found in post-mortems, in four patients who died of other causes. Despite a coarctation of the aortic isthmus, all the patients felt well and worked before the complication set in. Wright attributes the direct cause of the aneurysmal rupture to physical exertion. In our second patient the cerebral haemorrhage also occurred after a physical strain.

The existence of an aneurysm of a Willis' circle vessel aggravates the prognosis of the disease with which the patients could live quite long. A correct diagnosis may be made, if the possibility of such a combination is borne in mind. At any rate, if in the case of a subarachnoid or cerebral haemorrhage young people show symptoms of high arterial blood pressure, it is necessary to remember the possibility of stenosis of the aortic isthmus. On the other hand, the appearance of symptoms of acute disturbance of cerebral blood circulation in a case of stenosis of the aortic isthmus suggests the possibility of a ruptured aneurysm of a cerebral vessel. There are reports of a successful ligation of a ruptured aneurysm of the anterior cerebral artery in cases of stenosis of the aortic isthmus. The location of the aneurysm was established definitely by means of arteriography.

In addition to the described complications of the central nervous system which could be classified as focal lesions of the brain, the loss of consciousness and convulsions may often be observed in cases of congenital heart

diseases. Tyler and Clark observed in 1875 patients suffering from congenital heart diseases attacks of unconsciousness and epileptic seizures in 14.7 per cent of the patients with cyanosis and only in 3.1 per cent of the cyanosis-free patients. That is indicative of the great frequency of paroxysms in cases of mixture of arterial and venous blood.

Convulsions often occur in a cyanotic crisis arising spontaneously or caused by a slight physical strain. Paroxysms are caused by anoxia and are not associated with symptoms of focal brain lesions. However, if paroxysmal attacks are concomitant with symptoms of focal lesion in the central nervous system, the attacks may be caused by dilation of the cerebral veins, thrombosis of these veins, or old scars formed after arterial, or venous thrombosis.

Cerebral thrombophlebitis develops sometimes in patients suffering from congenital heart diseases with cyanosis, especially in cases of Fallot's tetralogy. Factors contributing to these developments are: dilation of cerebral veins, compensatory erythraemia and increased viscosity of the blood. Thrombophlebitis of this type develops after surgical operations as well.

The clinico-anatomical data mentioned here afford ground for the conclusion that in cases of congenital heart diseases we may observe, in addition to paradoxical embolisms, abscesses of the brain, aneurysms of vessels at the base of the brain, haemorrhages into the brain, thrombosis of the cerebral vessels and epileptic seizures. Evidence of these complications of the nervous system associated with congenital heart diseases often assists in correct diagnostics and in the correct choice of the necessary treatment.

RHEUMATIC ENDOMYOCARDITIS

Questions relating to the clinical picture, pathogenesis and pathomorphology of lesions of the nervous system in rheumatism, and in cases of rheumacarditis in particular,

have been thoroughly studied in the last 25 years by a number of authors (A. P. Avtsyn, V. K. Beletsky, M. O. Gurevich, V. V. Mikheyev, M. S. Margulis, T. P. Simson, E. K. Skvortsova, M. B. Tsuker and others). These investigations have revealed the exceptional polymorphism of the clinical picture of lesions of the nervous system in cases of rheumatism, and in cases of rheumatic endomyocarditis in particular. The formerly prevalent idea that embolisms of cerebral vessels occupy the main place among lesions of the nervous system associated with rheumocarditis was rejected. Frequently occurring vascular thrombosis is caused not by an embolus carried by the blood flow from the regions of the heart, but by vasculitis developing in the vascular wall. Thrombovasculitis is one of the manifestations of meningo-encephalitis in which proliferative inflammation elements predominate over exudative ones, while sclerosing begins early.

Cerebral Rheumatism. Clinical symptoms of lesions of the nervous system may originate simultaneously with symptoms of endomyocarditis, or in the case of its relapse; in most cases, however, symptoms on the part of the nervous system appear after weeks, months and years following endomyocarditis.

In the picture of acute, subacute and chronic rheumatic encephalitis rheumatic thrombovasculitis occupies the most prominent place (V. V. Mikheyev). In these cases, more or less acute manifestations hemi- or monoplegia, and less often—other focal symptoms of cerebral lesions develop. In some cases the disease begins with headaches, giddiness and vomiting. Disturbances of consciousness are moderate or altogether absent. In cases of thrombovasculitis of cortical branches of the cerebral arteries, epileptic seizures, often of the Jacksonian type, may be observed. The gravity and clinical development of thrombovasculitis depend upon the extent of the softening, its localisation and the patient's age. Sometimes only residual phenomena, such as mild hemi- or monoparesis may

be found in young people with a great capacity for compensation. In many a case symptoms of focal lesions of the brain disappear completely within a few hours. After this kind of restoration the fate of the patient depends upon the recurring cerebrovascular accidents which are characteristic of the development of a rheumatic lesion of the brain.

The clinical picture of encephalitis, or meningo-encephalitis may develop acutely, or subacutely. The disease begins with a rising temperature, headaches, in some cases —vomiting. A medical examination reveals a rigid occiput, Kernig's and Brudzinski's signs. A confusional state, stupor, pathological pyramidal signs, lesions of the cranial nerves, most frequently in the form of oculomotor disturbances may also be observed. Cases of choreiform jerks have also been described. According to M. B. Tsuker, they are distinguished from chorea minor by regular, rhythmic movements limited primarily to distal parts of the extremities.

Other syndromes such as haemorrhagic meningitis, the diencephalic syndrome with insomnia, pain, general hidrosis, trophic lesions of the skin and epileptic seizures are observed more rarely. In the last few years, Soviet psychiatrists have devoted much attention to cases of rheumatism with psychiatric disturbances which are quite variable. In the opinion of some authors, chronic rheumatism of the brain may manifest itself in the form of other mental diseases such as schizophrenia, maniac-depressive psychosis, or involutional psychosis (M. O. Gurevich, D. S. Ozeretskovsky, V. K. Skobnikova and others).

Numerous neuro-psychiatric clinical syndromes described in the last few years in cases of rheumatism indicate that the boundaries of the disorder have not been drawn distinctly enough. In each case it is necessary to show clearly the connection of rheumatism with the lesions of the nervous system. L. I. Gefter emphasises that pronounced rheumatic changes in different organs, the nervous system

included, are observed only in the case of an active process in the heart.

In histopathological examinations of the brain we have in the foreground a picture of vasculitis which affects most frequently small and medium-sized arteries. Proliferation of the endothelium and subependymal connective tissue is characteristic of this process. Infiltrations of lymphocytes and plasmocytes develop in the vascular walls and around them. An acute attack of rheumatism leads to the development of panarteritis with systemic leukocyte and monocyte infiltration of the vascular wall. V. K. Beletsky and A. P. Avtsyn observed in cerebral parenchyma a productive reaction of histiocytes, as well as microgliocyte nodules. Progressive endotheliosis may completely close up the orifice of the vessel with subsequent development of small patches of softening in the brain. Fragmentation of elastic tissue and fibrosis of the muscular coat of the artery may resemble similar processes in arteriosclerosis.

N. B. Mankovsky notes that rheumatic encephalitis may sometimes acquire a haemorrhagic character.

The long known forms of nervous lesions in rheumocarditis include embolism of the cerebral vessels and chorea minor. As stated above, V. V. Mikheyev, V. K. Beletsky and A. P. Avtsyn established that in cases of active rheumocarditis embolisms are much rarer than thrombovasculitis. They are more characteristic of rheumatic insufficiencies in the form of stenosis of the mitral valve with auricular flutter.

Embolism of Cerebral Vessels. The blocking of a cerebral vessel by an embolus leads to the rapid development of focal necrosis of the cerebral tissue. Macroscopically a focus of softening may be detected 24-48 hours after the appearance of the embolism in the form of a grey, irregular, vaguely outlined patch which is softer to the touch than the surrounding tissue.

It is usually believed that the left cerebral hemisphere is affected more frequently. This is explained by the fact

that the embolus is propelled more often through the left carotid artery which is a direct continuation of the superior aorta. This assertion is refuted by statistical data (M. I. Astvatsaturov, Jons) which show that both hemispheres are affected with practically equal frequency.

In 75-80 per cent of cases the embolus obliterates the orifice of the mid. cerebral artery, or its branches. The softening usually affects the forepart of the putamen, the caudate nucleus and the strip of the internal capsule between them. This softening is sharply bounded at the outer edge of the internal and external capsule. The islet and grey substance of the cerebral hemispheres may often be affected by the softening. The white substance of the hemispheres, the Pons varolii, the optic tract and the peduncles of the brain are affected much rarer. Cerebrovascular accidents usually occur suddenly, without any prodromal symptoms. The loss of consciousness is observed in 50-60 per cent of cases. In the majority of cases the coma is of shorter duration than in cases of haemorrhages and thrombosis. In embolisms of the cortical branches of the mid. cerebral artery epileptic seizures often of the Jacksonian type may be observed. Most frequently the embolus obliterates the orifice of the mid. cerebral artery. That leads to the development of hemiplegia of different degrees of gravity in combination with other disorders which depend upon the place and size of the cerebral softening. Embolism of the central artery of the retina is sometimes observed. Along with hemiplegia aphasia often appears in cases of sinistral embolism.

Chorea Minor. Chorea minor has long been known as a form of rheumatic encephalitis. It is observed almost exclusively in children between the ages of five and 15. The connection of chorea with rheumocarditis has been proved by many authors, although the frequency of rheumatism observed in cases of chorea, as given by different authors, ranges from 15 to 80 per cent. D. S. Futer discovered rheumatism in the past history of 25 per cent of his patients

and in 30 per cent during the disease. In 35 per cent of pregnant women suffering from chorea the anamnesis may reveal a case history of chorea minor in childhood. That offers the ground for assuming that chorea in pregnancy is a relapse of chorea minor.

The clinical picture of chorea minor is well known. The disease begins subacutely, or gradually. It often happens that before the appearance of convulsive jerks the child becomes irritable, capricious and restless. Characteristic features are involuntary, irregular jerks of the extremities, facial muscles and the tongue. Subsequently all the controlled movements are interrupted and become impossible. Usually, involuntary movements abate in sleep. At times choreic movements are most pronounced on one side (hemichorea), but even then they are not entirely absent on the other side.

The muscle tone of the extremities is low. Tendon reflexes may be abnormally high. When the patellar reflex is induced the quadriceps muscle remains contracted for some time and the shank remains stretched for several seconds (Gordon's sign).

Mental disturbances are almost always observed in the form of irritability and tearfulness; the patients are easily excited. A delirious state with confusion, excitability and hallucinations may be found in grave cases.

The temperature is usually normal, rarely subfebrile. Neutrophil mononucleosis or oesonophilia may be observed in the blood. Anaemia and loss of weight are frequently the case. Spinal fluid normal.

Histopathological changes in the cerebrum are moderate and not always detected. The described changes are not homogeneous in nature and localisation. A picture of diffuse encephalitis with changes in the minor vessels is characteristic of rheumatic encephalitis and is found most often. Lewy observed degenerative changes in the cells of the subcortical nodules. They are also found in the cerebral cortex, in the nigra substance, and in the dentate nucleus

of the cerebellum. M. S. Margulis believes that pathomorphological changes in the mesenchymal and ectodermal tissues are of an allergic nature and represent different phases of the same immuno-biological process.

The disease lasts from several weeks to several months and relapses often occur within several years in the spring and autumn months. The prognosis is favourable; usually, the disease may end in complete recovery, and relapses cease to occur after the age of 15-16.

ACUTE AND SUBACUTE SEPTIC ENDOCARDITIS

It is not our purpose to discuss various classifications of acute and subacute endocarditis, or to debate the identity or difference of their etiological factors. We shall confine ourselves to a description of complications in the nervous system which are common to septic endocarditis of differing etiology. Diamond found changes in the cerebrum of all the 13 cases of septic endocarditis studied by him. Features observed most frequently were miliary nodules composed of glia cells, lymphocytes, leukocytes and, in some cases, also of giant cells. Miliary abscesses, patches of softening connected with thromboembolism, punctuate haemorrhages, inflammatory and degenerative changes in the cerebral vessels have also been often observed. B. I. Mogilnitsky and K. A. Gornak emphasise the exceptional polymorphism of the pathomorphological changes observed in the brain in cases of protracted septic endocarditis. They found stases, thrombi, abnormally high permeability of the vascular walls, perivascular oedema and perivascular haemorrhages; in the vascular walls they observed swelling, plasmorrhagia, patches of necrosis, productive vasculitis and thrombovasculitis. Mycotic embolisms with developing aneurysm of the vascular walls, encephalitis and meningo-encephalitis are observed.

Micro-organisms carried into the brain together with the embolus proceed to propagate there and their histoly-

tic action may destroy the vascular wall. The result is a haemorrhage into the brain (Fig. 1.). It may also occur in the case of an abnormal permeability of a vascular wall conditioned by the hyperergic reaction. In this case the blood often penetrates into the subarachnoid space and the

Fig. 1. Septic endocarditis. Haemorrhage into the brain

patient reveals a meningeal syndrome: vomiting, headaches, occipital rigidity, Kernig's and Brudzinski's signs. A lumbar puncture shows a haemorrhagic or xanthochromic cerebrospinal fluid. In these cases a correct diagnosis is quite difficult. A thorough examination of the internal organs and symptoms of endocarditis is of decisive importance.

In very advanced cases of protracted septic endocarditis, a more or less pronounced occipital rigidity and Kernig's sign are observed quite frequently. There are corresponding changes in the cerebrospinal fluid expressed in high albumin content up to 0.5-1‰ and neutrophil pleocytosis up to 100 cells in 1 cm^3.

In some cases, nervous symptoms may be the first signs of protracted septic endocarditis. One of our patients,

24 years of age, was suddenly overtaken by sinistral hemiplegia. Distinct symptoms of endocarditis appeared only three months later. G. G. Sokolyansky and D. M. Gastev described a case of haemorrhagic meningo-encephalitis

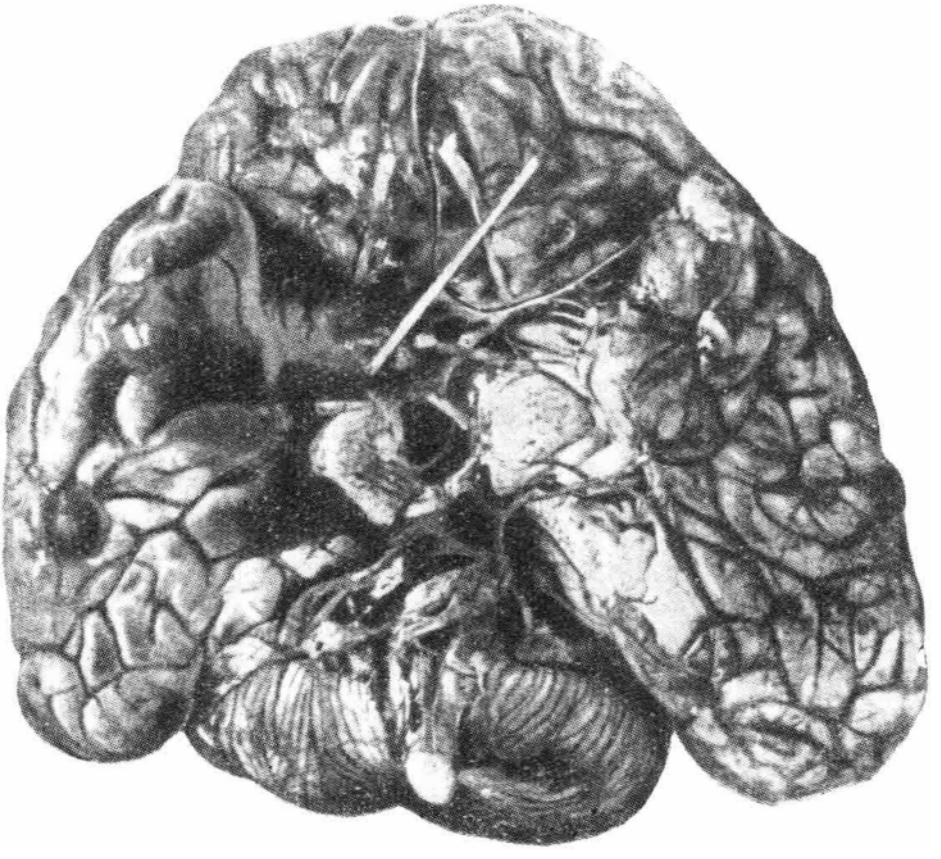

Fig. 2. Septic endocarditis. Ruptured mycotic aneurysm. Subarachnoid haemorrhage

where its connection with protracted septic endocarditis was discovered only at the autopsy.

Mycotic Aneurysms of Cerebral Vessels. The forms of cerebral lesions in cases of septic endocarditis described long ago include also mycotic, or embolic aneurysms. An infective embolus causes inflammation in the arterial wall and its sacculation, and in some cases leads to the formation of an aneurysm. (Fig. 2.)

A mycotic aneurysm which produces no clinical symptoms, or rarely produces symptoms of compression of the cranial nerves (ptosis, diplopia, oculomotor paralysis), may eventually rupture. It brings on sudden headaches, vomiting and brief attacks of unconsciousness. Convulsions are observed in some cases. Neurological examinations reveal occipital rigidity, Kernig's and Brudzinski's signs and, in rare cases, signs of lesions of the oculomotor nerves. Subarachnoid haemorrhage as a consequence of a ruptured aneurysm often leads to death. In a benign course of the disease a thrombus is formed in the aneurysmal sac with subsequent formation, whereupon the meningeal symptoms disappear gradually.

Cerebral Abscess and Purulent Meningitis. A singular cerebral abscess is exceptionally rare in the case of protracted septic endocarditis. Most frequently, numerous septic emboli from the endocardium form multiple miliary abscesses; a vessel blocked by bacterial masses may sometimes be found in the centre of an abscess. Necrosis of the cerebral tissue is observed primarily in the case of numerous embolisms of the small vessels. In such cases, a histopathological examination reveals various phases of abscess formation: a septic (coccal) embolus, perivascular necrosis of the cerebral tissue with a greater or lesser amount of disintegrating polynuclear cells and, lastly, completely formed abscesses (Fig. 3). The clinical picture in this case reveals symptoms of diffuse cerebral lesions without distinct focal symptoms.

A picture of purulent meningitis may develop when the infected particles of an embolus settle in the vessels of the pial cerebral membrane. Courville found a protracted septic endocarditis in 11 out of 337 cases of septic purulent meningitis.

Meningo-Encephalitis. Clinical symptoms of diffuse lesions of the brain, without distinct focal symptoms, are often observed in very advanced cases of endocarditis. Hyperergic vascular reactions, inflammatory and diffuse

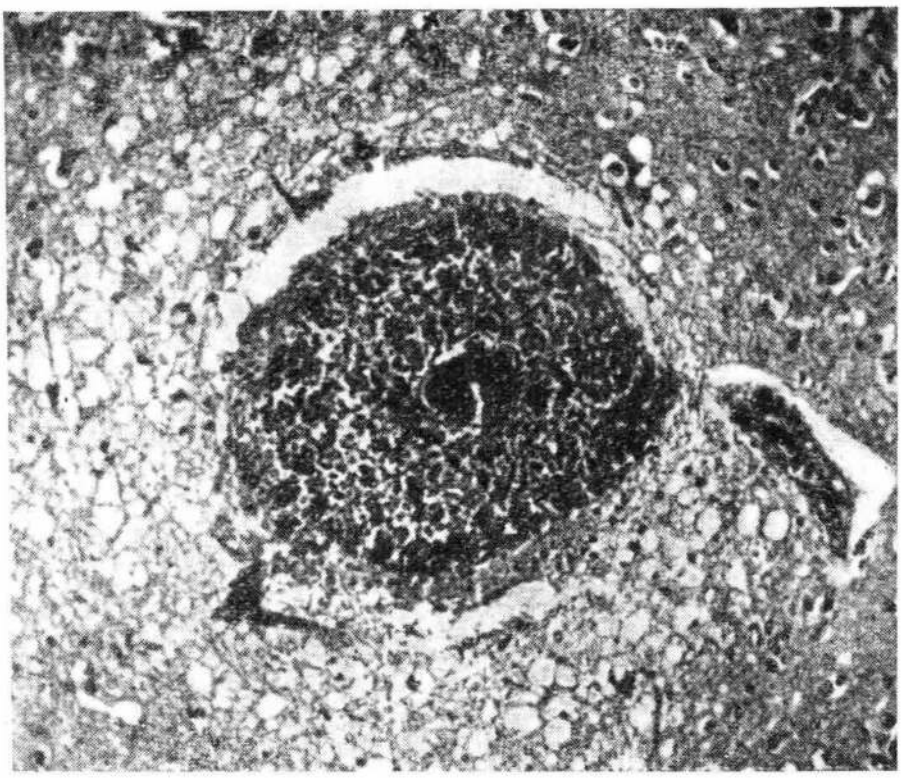

Fig. 3. Septic endocarditis. Microscopic abscess of the brain

toxic changes in the cerebrum may account for this. In such cases, distinctly connected with the vessels, diffuse degenerations of cortical cells and subcortical ganglia were found, along with endarteritis and focal parenchymatous changes. Changes in the cerebral cortex (necrosis, foci of desintegration with marked glial reaction) may also be explained by circulatory disorders. A histological examination reveals frequently glial nodules in the cerebrum which apparently represent a morphological expression of the local defence reaction against impacted micro-organisms.

In very advanced cases of septic endocarditis, characteristic features of the clinical picture of encephalitis and meningo-encephalitis are clinical symptoms of diffuse lesions of the brain with moderately expressed focal

symptoms (confusional states, excitation, meningeal symptoms, convulsions, coma). M. K. Usova observed meningeal symptoms in all the 12 cases described by her. An abnormally high amount of albumin and neutrophil pleocytosis were found in the cerebrospinal fluid of these patients.

STENOCARDIA AND THE ZAKHARIN-HEAD ZONES

Most prominent in the clinical picture of angina pectoris are paroxysmal pains in the region of the heart, behind the sternum, which radiate into the left shoulder and arm down to the little finger. Pain is felt also in the region of the left shoulder blade, left side of the neck and occiput, in the lower jaw and teeth. Pain radiating from the heart travels along the left sympathetic collateral trunk, intercostal nerves and left brachial plexus. Upwards pain travels along the centripetal fibers of the vagus and the cervical part of the sympathetic trunk.

Reflected impulses from the heart may be expressed also in other vegetative symptoms, such as perspiration, pallor and vomiting. A "vegetative storm" may burst in severe cases when nausea, vomiting and profuse perspiration are combined with headaches, giddiness, chills, retention of urine followed by diuresis. Moreover, the patient is possessed by morbid fear.

Pain in stenocardia is concomitant with hyperaesthesia in the Zakharin-Head zones. According to Head, a painful stimulation emanating from the viscera is felt not where it has originated, but distally on the surface of the body, in the zone innervated from the same spinal segment. In order not to return again to this question, we should like to dwell in somewhat greater detail on the general problem of the Zakharin-Head zones. Just as in the case of angina pectoris, lesions of other visceral organs are often attended by pain on the surface of the trunk and extremities. These zones correspond to the root distribution of sensi-

tiveness and to the zones along which the herpetic girdle is spreading.

Head established definite relationships between the viscera and the cutaneous segment innervation. According to Head, the III and IV cervical segments, the II-VIII thoracic segments, and, perhaps, the I-IX thoracic segments correspond to the heart; the III cervical, VII-IX thoracic, and, perhaps, the I and IX thoracic segments—to the stomach; the IX-XII thoracic—to the intestines; the III and IV cervical, VII and IX thoracic—to the liver; the VIII and IX thoracic to the gall bladder, the X-XII thoracic segments to the kidneys and ureters. Head's zones have been found also in the region of the head. Pain in the temporonasal region is indicative of lesions of the lung apexes, stomach, liver, aortic orifice; pain in the mid-orbital region is indicative of lesions in the lungs, heart and superior aorta; pain in the temporal region—of lesions in the lower lobes of the lungs, and cardia of the stomach; pain in the sincipital region—of lesions in the pyloris and upper intestines. In addition to spontaneous pain in the mentioned regions, a sensorial examination reveals hyperaesthesia, or hyperpathia.

Several theories have been proposed for the explanation of this phenomenon, the most widely accepted being Mackenzie's concept, according to which a morbid impulse from a visceral organ travels along the peripheral neuron to the corresponding segment of the spinal cord. Here the peripheral neuron enters into contact with the intercalary neuron and the latter is connected with the neuron which conducts cutaneous sensory impulses from the same metamere. A morbid visceral impulse induces in the gray substance of the corresponding spinal segment a focus of excitation in which the stimulation threshold becomes lower. In consequence, a nervous stimulation originating in the visceral periphery produces referred pain on the surface of the body. Pronounced excitation of the spinal segment prevails for a definite space of time during which the

threshold of excitation remains low. This phenomenon was defined by Mackenzie as the viscerosensory reflex. Similar explanations are given also for spastic muscle contractions observed in some cases (the visceromotor reflex).

A study of the conduction of visceral pain was made in cases of stimulation and removal of sympathetic trunks in ill people. Bentley and Smithwick have made a series of investigations in cases of hypertensive diseases before the lower thorax and first lumbar sympathetic ganglia. They established that pain in the epigastric region induced by blowing up a rubber bag placed in the duodenum disappears to the right of the median line in the case of a dextral operation, and it completely disappears after a bilateral denervation. Leriche and others stimulated the coeliac nerves during an operation performed under spinal anaesthesia. Pain appeared thereupon in the upper section of the shoulder blade. During operations on patients suffering from stenocardia, Leriche and Fontaine were irritating the stellate ganglion. In these cases the patients complained of a feeling of painful pressure in the chest around the region of the heart.

The mechanism of the disturbance originating in a visceral organ and causing cutaneous pain is still not clear. Leriche believes that an impulse passing along sympathetic fibers produces in the skin disturbances of vasomotor innervation which are responsible for changes in the state of excitability of the nerves. According to L. A. Orbeli, referred pain in cases of diseases of the viscera originates as a result of the transmission of impulses from a visceral organ along the axonal connections of the sympathetic nervous system to the corresponding metameres of the body. Permanent irritation of a given cutaneous metamere causes hyperalgesia which should be regarded as a trophic adaptation phenomenon. Pollock points out that irritation of visceral effector endings leads to the formation of metabolites. The mechanism of referred pain is not always

the same. The range of its propagation varies and the pain depends upon the organ where it originates. For example, two types of pain should be distinguished in diseases of abdominal organs: real visceral pain and referred pain. The former is felt deep inside; it cannot be definitely localised; it is felt along the median line of the body, at a level corresponding to the embryonal segments from which the affected organ has developed, irrespective of its location in the adult person. This pain is conditioned by afferent impulses emanating from this organ. When the pathological process approaches the parietal surface of the peritoneum, the second type of pain appears; it is conditioned by irritation of the somatic nerves of the abdominal wall. The latter pain may be accurately localised and it corresponds to the place of the pathological process.

In this case hyperaesthesia of the cutanea and muscle spasms develop. For example, in the case of acute appendicitis, when the process is limited to the appendix, poorly localised epigastric pain and very mild muscular tension is found; but when the process spreads so as to irritate the peritoneum, the pain is localised right over the appendix and hyperaesthesia and local muscular spasms appear. Numerous observations have shown that the internal organs are relatively insensitive to irritations conditioned by an incision, cauterisation, or scratching, and that an effective stimulus for true visceral pain is the extension or spasm of the smooth muscles in the walls of the hollow visceral organs. However, this rule cannot be fully applicable to pain emanating from the heart and aorta. This pain resembles in many respects the pain radiating from the parietal peritonium.

The question of the diagnostic value of the Zakharin-Head zones has come up for discussion again and again. This is explained by the fact that Head's zones are not absolutely constant. They may vary in localisation and intensity in different patients. These zones represent an individual reaction which is indicative of possible varia-

tions of the metamerisation of the visceral organs and their diverse excitability. As Head himself noted, visceral stimulations may be generalised. In some cases the pain spreads over half of the body; in this case pain and hemihyperaesthesia may be detected by pressing over the entire half of the body (A. N. Geimanovich and G. D. Leshchenko). Viscerosensory reflexes, which manifest themselves most frequently and vividly in cases if stenocardia, vary in localisation. Along with frequently observed pain in the left part of the chest, along the ulnar edge of the left arm and wrist, there are cases when pain originates in the shoulder blades, neck and lower jaw. In some cases, pain is referred in the region of the lower ribs, simulating a state of an acute abdomen.

Dwelling on these facts Leriche subjected the theory of Head's zones to severe criticism and came to the conclusion that they appear by far not in all cases of visceral lesions and that quite frequently their location does not correspond to Head's zones. Leriche maintains that the localisation of these zones remains inexplicable in the light of our anatomical and physiological knowledge. A. M. Grinstein believes that the polymorphism of the Zakharin-Head zones is explained by the existence of two pathways of viscerosensory impulses. In particular, as regards Head's zones in cases of stenocardia, A. M. Grinstein points out that the fibers entering the spinal cord at the level of the I and II thoracic segments become connected there with the cells of the lateral horn of this level, and the latter direct fibers towards the head. This explains the appearance of Head's zones also in the head. According to A. M. Grinstein, the participation of thoracic visceral innervation tends to spread Head's zones to the level of the IV-VII ribs.

Noteworthy, along with the diffuse character of the pain, it must be stressed that localisation of the pain may differ, depending upon its origin in the atria or ventricles of the heart. Pain emanating from the ventricles, as in the

case of stenocardia, frequently radiates into the upper part of the chest and internal surface of the upper extremities, i.e., into regions corresponding to the I-III thoracic segments. Pain referred from the atrium into the lower section of the thorax corresponding to the IV-VI thoracic segments. The explanation of this is found in the phylogenesis of the heart. In animals the ventricle is located in front of the atrium and is innervated by segments lodged in the spinal cord more orally.

In some cases of stenocardia visceromotor reflexes are expressed in spastic movements of the upper extremities and intercostal muscles. I. I. Rusetsky found a tonic tension in the intercostal D_2-D_4 muscles in the left forepart of the chest surface in 50 per cent of patients suffering from stenocardia.

A rise in the tone of the sternocleidomastoid and trapezius muscles is observed more rarely. Pain in the Zakharin-Head zones is in some cases combined with sensitiveness to pressure of the shoulder plexus and may be mistaken for neuralgia of the plexus or for occipital and intercostal neuralgia. Unlike the latter, cardiac pain is concomitant with depression, fear of death, pallor in the face and absence of sensitiveness to pressure on Valleix's points.

MYOCARDIAL INFARCTION

For a long time embolism into the brain from a mural thrombus was considered the only complication of the nervous system in myocardial infarctions. Recent investigations have shown that lesions of the nervous system associated with myocardial infarctions are not limited to embolisms, that they are quite frequent and may be concomitant with the beginning of the infarction or appear at different periods of the disease (Z. N. Dracheva, L. B. Litvak, M. Y. Melikova, D. I. Panchenko, Bean, Read and others).

Cerebral lesions in myocardial infarctions call forth the appearance of systemic and focal cerebral symptoms. Systemic cerebral symptoms are expressed in the first place by the intensification of the symptoms usually accompanying myocardial infarctions: psychomotor anxiety, fear and confusional state. A delirious state, epileptic seizures and various degrees of loss of consciousness (from transient fainting to a coma) may be observed in some cases.

Symptoms of focal disturbances of cerebral blood circulation appear most frequently a few days after the development of a myocardial infarction. They are usually expressed in hemiplegia and hemiparesis. Paralysis of an extremity, or an epileptic seizure are much rarer.

Focal lesions of the brain in myocardial infarctions may be caused by various factors: 1) embolism from a perimural thrombus; 2) thrombosis of cerebral vessels; 3) disturbances of the blood circulation without any vascular obstruction. On the basis of post-mortem examinations in cases of myocardial infarction it is often hard to distinguish a cerebral embolism from thrombosis.

In the last few years it has been emphasised, in Soviet literature especially, that the concept of "embolism" does not reflect the nature and pathogenesis of extracardial vascular lesions in myocardial infarctions. In this connection, there is an increasing tendency to define these lesions as thrombo-embolisms. Distinct atherosclerotic changes of the arterial wall are found in the affected parts. A blood vessel may often be blocked even in the absence of sources of an embolism in the form of thrombotic deposits in the heart. Lastly, clinically it is often impossible to distinguish an embolism from thrombosis. According to A. N. Berinskaya, N. V. Kalinina and T. I. Meyerzon, thrombo-embolisms of cerebral vessels are observed in 26.2 per cent of the cases of thrombo-embolism in myocardial infarctions. It should also be borne in mind that a considerable fall in arterial pressure and in the minute volume of blood, a cerebral softening may appear even in

the absence of an embolism or thrombosis. Even in the case of focal cerebral lesions it is frequently impossible to find any obstruction of a cerebral blood vessel. The decisive role in such cases is played by hemodynamic factors. That applies especially to cerebral symptoms which appear simultaneously with a myocardial infarction. M. Y. Melikova found symptoms of disturbances in cerebral blood circulation at the beginning of the disease in 41 out of 130 cases (31.4 per cent) of myocardial infarctions. In almost all the cases these disturbances were transient and were expressed by the loss of consciousness, vomiting, giddiness, headaches, aphasia and disturbances of vision. Only in one case was there a stable hemiparesis.

V. V. Utkin found disturbances of cerebral blood circulation in 28 out of 560 patients affected with myocardial infarction. Analysing the archive materials on 212 cases of myocardial infarction, L. I. Sapir found symptoms of disturbances in cerebral blood circulation in 32 cases. In 22 of these cases, cerebral symptoms appeared simultaneously with anginal attacks, and in the remaining 10 cases—at different periods after the development of the infarction. In 20 cases, headaches, nausea, vomiting and transitory loss of consciousness were observed at the beginning of the disease. In three of these cases focal symptoms appeared in the form of visional disturbances, hemiparesis and Jacksonian epileptic seizures. All these symptoms disappeared rapidly, with the exception of two cases where a stable hemiparesis developed.

In some cases a state of coma is observed with rapidly developing hemiplegia; it may be preceded by one or several paroxysmal epileptic seizures. Usually, but not necessarily, the appearance of hemiplegia is accompanied by a coma.

During histological examinations of the brain of nine persons who died of myocardial infarction, M. Y. Melikova found symptoms of stasis, oedema and minor diapedetic haemorrhages in the brain. Race and Lisa studied 15 such

cases and found massive softenings in two cases, focal softenings in five and multiple petechial haemorrhages in seven cases. (Fig. 4.)

The question of the pathogenesis of disturbances in cerebral circulation in the initial stage of myocardial infarction is insufficiently elucidated. N. K. Bogolepov

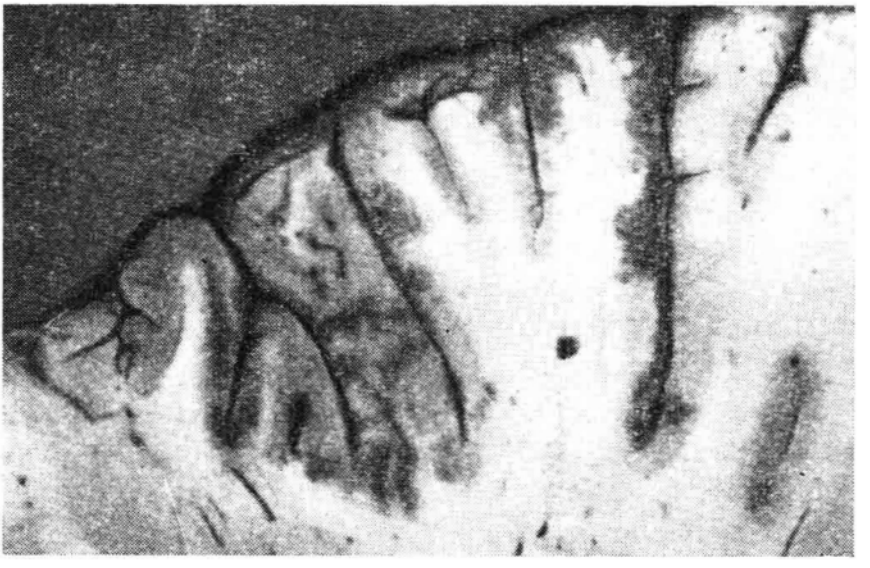

Fig. 4. Myocardial infarction. Multiple punctuate haemorrhages into the cerebral cortex

believes that the stimulation of the interoceptors of the heart is followed by a reflectory spasm of cerebral vessels which leads to cerebral anoxia. In his opinion, disturbances in cerebral circulation occur most frequently in cases of infarction of the anterior lateral septum of the left ventricle, which is explained by the specific nature of innervation in this region of the heart. The region of vascularisation of the descending branch of the coronary artery is the area from which the reflex to the vessels of the stem originates. That is facilitated by the connection of the anterior cardiac plexus with the aorto-carotid zone which transmits impulses to the vasomotor centres of the

cerebrum. Major importance is attached to the neuro-reflex mechanism and to angiospasms also by Z. N. Dracheva, G. A. Rayevskaya and M. Y. Melikova.

An important part is played by haemodynamic factors, and, primarily, by a fall of general arterial pressure as a result of myocardial infarction and reduction in the minute volume of the heart which causes a deficiency of cerebral blood supply. A similar clinical picture and similar histopathological changes in the cerebrum may also be found in other diseases which cause a deficiency in cerebral blood supply: paroxysmal tachycardia, Adams-Stokes syndrome, ventricular fibrillation, surgical shock with a fall of arterial pressure in elderly people and a great loss of blood. Putnam and Rothenberg proposed the term "cerebro-vascular insufficiency" for such cases, and it has now won wide recognition.

In addition to the fall of arterial pressure, there are other important hamodynamic factors: decelerated blood flow, rapid decline in the mass of the circulating blood. Lastly, an unquestionable role is played by changes in the physical and chemical properties of the blood, such as abnormally high coagulability, etc.

Due to administration of anticoagulants in medical practice, there has been a considerable decline of thromboembolisms in cases of infarction in different organs, including cerebral softenings.

The following example is illustrative of the correlation of cerebral lesions with the fall of general arterial pressure.

Patient K., 58 years of age, was admitted to the hospital on February 27, 1948 with complaints of severe pain in the region of the heart, dyspnoea and paralysis of the left extremities. During the previous four years he had been treated for the hypertensive disease. For two years he had been suffering from attacks of pain in the region of the heart radiating into the shoulder blade and left arm. On February 27, in the street, he was suddenly overtaken by a severe pain in the chest and abdomen, and soon lost consciousness. When he recovered consciousness the pain in the chest persisted;

he could not move his left extremities. On the same day he was brought to the hospital.

At the time of his arrival the patient was in a state of clouded consciousness and could barely answer questions. Pulse rate—104 beats per minute, blood pressure 100 60 mm Hg, slight dilation of the heart to the left. Extrasystole arising from time to time. Left corner of the mouth drawn down. Sinistral hemiplegia and hemianaesthesia. Tendon reflexes accentuated in the left extremities. Sinistral Babinski's sign. Electrocardiographic picture typical of a fresh infarction of the anterior myocardial wall. The patient died two days later.

Pathological diagnosis: Sharply expressed atherosclerosis of cerebral vessels, heart and kidneys; infarction of the anterior septum of the left ventricle of the heart spreading to the interventricular septum; extensive patch of softening in the right cerebral hemisphere. No thrombus found in the orifice of the cerebral arteries.

The simultaneous appearance of symptoms of myocardial infarction and of a cerebrovascular accident makes it possible to exclude a cerebral embolism in this case. The absence of a thrombus in the cerebral vessels supports the conclusion that the softening in the brain resulted from acute cardiac insufficiency with a severe fall of arterial pressure.

The significance of a fall of general arterial pressure in the development of a cerebrovascular accident is proved by E. N. Kosmarskaya's experimental investigations. When a cerebral vessel in a dog was compressed with a silver clip, oedema and cerebral softening never reached any considerable proportions, but when the arterial pressure of the animals was artificially reduced (before or after the closing of the orifice of a cerebral vessel), they perished during the first day after the operation. When a cerebral vessel in a dog was disconnected after a reduction in the general arterial pressure, necrosis in the region of the mid. cerebral artery developed in addition to a general oedema of the cerebral matter.

A similar experiment was performed by Thompson and Smith on monkeys. They closed the orifice of the mid. cerebral artery with a clip. In case the general arterial blood pressure remained normal, no clinical, electroencephalographic and pathological changes were found in the

brain of the monkeys; but the closing of the orifice of the mid. cerebral artery followed by a considerable fall of the general arterial pressure, resulted in hemiplegia, distinct electroencephalographic disturbances and extensive patches of softening in the cerebrum.

The mentioned facts are quite convincing, showing that an acute cardiovascular insufficiency may be caused by both transient and stable disturbances in the cerebral blood circulation. A state of coma and hemiplegia may disguise a myocardial infarction which may be discovered unexpectedly in a post-mortem examination. Dozzi found in eight out of 26 cases of hemiplegia a myocardial infarction which produced no clinical symptoms. In 100 post-mortem examinations following cerebrovascular accidents, Race and Lisa found myocardial infarctions in 15 per cent of the cases. In some instances, a carefully studied case history makes it possible to establish that cerebral symptoms had been preceded for some time by pain in the region of the heart. A frequent, weak pulse and a fall of arterial pressure in the case of a cerebrovascular accident should warrant the assumption of a myocardial infarction. In all such cases an electrocardiogram must be made. In general, mistakes of this kind have become much rarer with the introduction of electrocardiography into clinical practice.

Shoulder-Hand Syndrome. In some cases, pain in the shoulder and trophic disturbances in the hands, mainly in the left one, appears in patients 2-10 weeks, and sometimes a few months, after a myocardial infarction. The authors who described these disturbances defined them as the shoulder-hand syndrome following myocardial infarction (Edeiken, Steinbrocker). Trophic disturbances in the shoulder joints, confirmed by X-ray examinations, were described by K. G. Yerusalimchik, M. D. Khvesina and A. G. Tetelbaum.

Pain, sensitiveness to pressure, stiffness of one or both shoulder joints appear mainly 2-10 weeks after the development of a myocardial infarction. That may be fol-

lowed by pain in the wrists and fingers, stiffness, swelling and in some cases also by pallor of the wrists and fingers. In fewer cases, a tendency towards flexural contracture, resembling Dupuytren's contracture, may be observed in the fingers.

A complete clinical picture of the shoulder-hand syndrome is rare. Ordinarily, the pain is restricted to the shoulder; it is observed on one side and is not accompanied by objective symptoms. Thus far no correlation has been observed between the localisation, extension and gravity of the infarction and the appearance and severity of the shoulder-hand syndrome.

The development of this syndrome is apparently caused by the long absence of movements in the hand and the abnormal tension of muscles of the shoulder girdle, owing to long immobility of the bed-ridden patient. K. P. Dyadkin believes that changes are produced by the neurodystrophic process conditioned by a stimulus coming from the heart. In support of this hypothesis he mentions the development of trophic changes in the bones not only in cases of infarction, but also in stenocardia. Edeiken believes that pain in the hand is a referred pain resulting from causalgia produced by the nerve fibers involved in the heart cicatrix. He points out that the accidental induction of sympathetic fibers into the cicatrix may explain the appearance of the shoulder-hand syndrome only in some cases of myocardial infarction, as well as its appearance several weeks after the infarction.

The prognosis in the case of the shoulder-hand syndrome is usually favourable, but the pain may persist for several months. Recommended treatment includes sympathectomy, blockade of the cervical sympathetic ganglion, etc. Our experience has shown that equally successful results may be achieved by local heat applications, analgetics and medical gymnastics.

CHRONIC CARDIAC INSUFFICIENCY

Patients suffering from chronic cardiac insufficiency in the initial stage of the disease often complain of high fatigability, decreased physical and mental efficiency, headaches and insomnia. With the development of symptoms of cardiac insufficiency and growing deficiency of oxygen, lactic acid, ketone bodies, unsaturated acids and other inadequately oxidised products of chemical metabolism accumulate in the blood. Changes in the nervous system in very advanced cases of chronic cardiac insufficiency are due not only to hypoxia, but also to autointoxication with products of natural and pathological metabolism. Scheinker distinguishes four types of cerebral lesions in chronic cardiac insufficiency: 1) vasothrombosis with numerous haemorrhagic infarctions; 2) cerebral embolism; 3) numerous focal patches of softening; 4) diffuse lesions of the cerebral cortex.

In a detailed pathomorphological examination of the brain of 20 patients who died of chronic cardiac insufficiency, Scheinker and Kuhr found in the cerebral cortex diffuse foci of haemorrhagic infarctions. The underlying white substance of the brain was oedematic. Thrombosis of many minor veins was found in the regions of the haemorrhagic infarction. Other veins were dilatated with distinct symptoms of stasis. Marantic thrombosis of the cerebral sinuses and cortical veins were observed in some cases. Numerous minor haemorrhages were sometimes found in the cerebral tissue. The most probable cause of this type of thrombosis is a deceleration of the blood flow in the brain, obstruction of the return flow of venous blood and abnormally high coagulability of the blood. Lastly, in some cases chronic cardiac insufficiency leads to the development of mural thrombi in the heart, chiefly in the auricula sinistra, which may become a source of embolism into the brain. These embolisms spread in some cases to both hemispheres.

In cases of chronic cardiac insufficiency, major and

minor patches of softening in the brain are observed also in cases when there is no blocking a vessel by an embolus or thrombus. The cause of this type of softenings lies in the disturbance of haemodynamics expressed in a deceleration of the blood flow and fall of the minute volume of blood which leads to the reduction of the blood supply of the cerebral tissue. A definite role is played in this case also by a decline in the return blood flow to the right heart. The disturbances of blood circulation is expressed especially in those regions of the brain where the arterial walls have lost their elasticity in consequence of sclerotic changes. In the case of highly pronounced stasis in the lungs there is a greater possibility for the formation of focal softenings in the brain due to inadequate oxidation of the circulating blood.

PAROXYSMAL TACHYCARDIA

Nervous symptoms are observed in 20-30 per cent of the cases of paroxysmal tachycardia. Their frequency depends apparently upon the form of paroxysmal tachycardia which, in its turn, is known to depend upon the localisation of the occurring impulse. Barnes found cerebral symptoms in 60 per cent of the cases of ventricular paroxysmal tachycardia, in 25 per cent of the cases of auricular tachycardia and in 41 per cent of the cases of sinus tachycardia.

Nervous symptoms are secondary symptoms and depend upon the insufficiency of cerebral circulation developing during an attack. Owing to an excessively frequent contraction of the heart, its ventricles are not filled up sufficiently with blood and that leads to the reduction of the blood supply to the brain. Cerebral anaemia is the cause of nervous symptoms in paroxysmal tachycardia. These symptoms are more frequently observed in elderly people, inasmuch as atherosclerosis of the cerebral vessels during an attack makes cerebral anaemia more pronounced.

Nausea and vomiting may appear at the very beginning of an attack. This is followed by general weakness, paraesthesia, stretching pain in the legs, giddiness, disturbances of vision in the form of transient blindness or scotoma, loss of consciousness and, in some cases, convulsive seizures.

In rare cases the nervous symptoms are focal, expressed in aphasia, hemiparesis, or local paraesthesia. These focal symptoms are due to disturbances of the blood circulations in separate regions of the brain, which are evidently explained by highly pronounced atherosclerosis in these regions. Along with the above-mentioned symptoms, fear, depression and excitation, combined in rare cases with a state of delirium and sometimes hysterical reactions, may be observed.

Some of these nervous symptoms tend to remain more or less constant during each successive attack. The appearance of these symptoms does not affect the prognosis in paroxysmal tachycardia which usually remains favourable.

In forms which are not very pronounced, nervous symptoms such as fear, giddiness and loss of consciousness may predominate in the picture of the disease and obscure its essence. That happens especially often when the patients pay no attention to tachycardia, considering it the result of giddiness, nausea, etc. In some cases an attack may occur at night and evoke a suspicion of epilepsy. It should be emphasised that neurasthenic and hysterical symptoms associated with paroxysmal tachycardia are not the cause, but a consequence of the disease.

Paroxysmal tachycardia is well known to therapeutists, but it usually is overlooked by neurologists. If a disturbance of consciousness occurs during an attack, the disease may be erroneously diagnosed as epilepsy. The following observation may be given as an example.

Patient, 32 years of age, had been suffering from attacks for five years. Attacks used to begin with giddiness and palpitation; she

would manage to lie down, but then lost consciousness. She had never had any convulsions during an attack, but muscular rigidity had been observed. An attack lasted from a few minutes to two hours. The patient had been treated for epilepsy. An examination during an attack disclosed tachycardia, heart rate up to 200 beats a minute; the subsequent electrocardiogram revealed a dextroventricular type of paroxysmal tachycardia.

Usually the presence of tachycardia is established by questioning and an objective examination. In some cases, when attacks are associated with the loss of consciousness, it is necessary to make a differential diagnosis between epilepsy and tachycardia. The absence of spontaneous urination and fecal incontinence are indicative against epilepsy. The patient does not fall down, but manages to reach the bed. During the attack the face is pale and not cyanotic as in epilepsy. There is no feeling of jadiness, no headache, or drowsiness after the attack. Of major importance is the determination of tachycardia during an attack, and the changes found in the electrocardiographic curves.

HEART BLOCK AND THE MORGAGNI-ADAMS-STOKES SYNDROME

In cases of a complete atrioventricular block, or atrioventricular dissociation, there is a marked deceleration in the rhythm of the ventricular contractions with a resulting deficiency of the cerebral blood supply. Cerebral anaemia brings on attacks known as the Morgagni-Adams-Stokes syndrome.

The clinical picture is characterised by sudden giddiness, dimness of vision and a transient loss of consciousness. It often happens that the attack is so brief that it passes before the patient falls down.

In graver cases, the patient loses consciousness and falls down, with a stop of respiration, his face grows pale, his lips become cyanotic, the cervical veins swell up. The eyes are motionless and rolled up, the pupils dilated, jerks of

facial muscles and extremities appear, and in some cases an epileptiform seizure, frequently with uncontrolled urination and defecation, is observed. An attack may be preceded by a choking sensation and fear. The number, gravity and duration of attacks vary greatly and depend upon the degree of bradycardia.

Clark observed in a patient jerks only of the eyes and fingers when heart contractions were retarded by 6-8 seconds. Longer retardation called forth the complete loss of consciousness. These observations were confirmed by the experimental investigations of Erlanger and Blackman who provoked a convulsive seizure by pinching the His bundle and retarding the cardiac activity by 15-20 seconds only. In the case of Vaquez an arrest of the heart systole by three seconds caused giddiness, by 7-8 seconds—a faint, and by 12-15 seconds—an epileptiform seizure. Menière produced a convulsive seizure by pressing upon the eyeballs and thus retarding the systolic function by 15 seconds. M. A. Balaban described two cases in which an Aschner's reflex test produced an epileptiform attack.

The rapid progress of thoracic surgery and operations on the heart made it possible to observe more frequently cases of retention in heart activity. A retention of 20-30 seconds extinguishes cerebral impulses and a delay of 6-10 seconds brings on a state of coma. Restoration of the blood circulation not later than 100 seconds thereafter leads to the rapid restoration of consciousness without any objective symptoms of disturbances in the central nervous activity. A prolonged anoxia leads to oedema of cerebral tissue, vacuolisation and necrosis of the cerebral cells. It has been established that philogenetically young parts of the cerebrum are more sensitive to anoxia. Necrosis of the cells in the IV and V strata of the cerebral cortex may set in five minutes after anoxia, in the cells of the midbrain—10 minutes after and in the medulla oblongata—only 20 minutes after that.

A differential diagnosis with epilepsy is of practical

value to the neurologist. The diagnosis is made on the basis of a marked retardment of the pulse and of the discovery of dissociation between the ventricular and atrial systoles.

An important factor is an electrocardiographic examination which brings out the existence of dissociation between auricle and ventricular systoles. It should be remembered that the above-described symptoms may be observed not only in pronounced forms of the Morgagni-Adams-Stokes syndrome, but also in cases of transient bradycardia and latent disturbances of the cardiac rhythm encountered in intoxications, in reconvalescents after infectious diseases. The actual cause of vague epileptiform seizures and loss of consciousness may be found in some cases by a careful examination of the cardiovascular system, by an electrocardiographic examination. It stands to reason that the usual anti-epileptic treatment is useless in this case. Atropin may cut short the block and thus relieve the patient of epileptiform attacks.

ANEURYSM AND AORTIC THROMBOSIS

Aortic aneurysm may influence the surrounding tissues, as well as the adjoining nerve trunks not only by pressure and dislocation, but also by involving into the inflammatory process and cicatrising the connective tissue cells around the aneurysm. Neuralgic pain is observed in more than 50 per cent of the cases, its localisation depending upon the location of the aneurysm and the affected nerves. Neuralgia is in some cases the first and only symptom of an aneurysm. Aneurysm of the ascending aorta is accompanied by girdle pain and stretching pain which radiates into the left shoulder blade and shoulder. Ordinarily, this pain does not submit to anti-neuralgic treatment; it has a pulsating nature which weakens or disappears at times when the patient is placed in a definite position, inasmuch as this position relieves pressure upon the nerve.

Vagus nerves pass on both sides of the aorta. After entering the thorax they branch out into recurrent nerves extending towards the larynx. The dextral recurrent nerve extends around the dextral subclavial artery, and the sinistral—around the aortic arch. Furthermore, the sinistral sympathetic trunk comes into contact with the descending part of the aorta. These topographical relationships explain the nervous symptoms produced by a growing aneurysm depending upon its location.

In the case of a sufficiently large aneurysm, or its location in the aortic arch, symptoms of compression of the recurrent nerve appear, and dyspnoeic attacks, difficulties in swallowing, coughing and hoarseness are observed. Symptoms of paralysis of the recurrent nerve appear, following these symptoms of irritation, and in some cases, even without them. It should be borne in mind that most usually paralysis of the sinistral recurrent nerve appears producing few symptoms and in some cases it can be discovered only by a thorough laryngoscopic examination. Phonation is preserved by compensation on the part of the dextral vocal chord; only at times does the voice become high, or hoarse.

Compression of the sinistral recurrent nerve may at first call forth irritation in the form of tachycardia. Subsequently paralysis of the nerve may induce bradycardia.

The vagus is involved in the process in much fewer cases, and it is accompanied by attacks of accelerated respiration, suffocation and fits of paroxysmal coughing. Irritation of the cardiac branches accelerates the pulse.

Compression of the sinistral sympathetic trunk leads to the appearance of the Bernard-Horner syndrome on this side. Incessant hiccoughing and one-sided paralysis of the diaphragm are observed when the diaphragmal nerve is compressed. Hyperhydrosis is slightly lower on the left side of the face, while the right one is less hyperemic. The Bernard-Horner syndrome is often observed, especially when the first cervical sympathetic ganglion is involved.

In some cases, the walls of an aneurysm, contiguous to the vertebrae lead to their injury and destruction, penetrate into the cerebrospinal canal, compress the spinal cord and produce a picture of compression myelitis. In such cases the disease may be mistaken for a tumour, or syphilitic myelitis. Serial X-rays may furnish the basis for a correct diagnosis.

Changes in the nervous system in cases of dissecting aortic aneurysm and local dilatation of the aorta with a haemorrhagic effusion into the aortic wall are less known. Should an adventitial rupture occur at the same time, that will rapidly bring on death due to an extensive haemorrhage.

When the haemorrhage is limited to the aortic wall and spreads along it, a clottage of the major aortic branches is the result. In these cases severe pain appears suddenly in the chest, radiating into the head, the jaws, neck, abdomen, arms, and, less frequently, into the legs. Cerebral symptoms may appear when the haemorrhage extends to the carotid artery. Paralysis of the extremities and spinal symptoms develop when the aa. iliaca, brachialis, and intercostalis are drawn into the process (of clotting). Nervous symptoms were observed in 45 out of 300 cases of aneurysm described in literature. (Adams.)

Our observation given below may serve as an example.

Patient P., age 60, had been under medical observation for the last five years on account of the hypertensive disease. Awakening one morning in December 1948, he felt sudden severe pain in the chest which spread to the abdomen and back, and he was forced to lie down again. Some time later the pain relaxed a little. Attempting to rise, the patient felt an unusual weakness and numbness in the left leg; paraesthesia appeared also in the right leg, but the leg was not as weak as the left one. On the following day the pain in the back became more intensive and the patient was taken to the hospital.

On arrival the patient was found to be suffering from flaccid paralysis of the lower extremities with the absence of the patellar and Achilles tendon reflexes and conductive disturbances of all forms of sensitiveness beginning from the level D_{8-9}. An examination of

the cerebrospinal fluid revealed no deviations from the normal. Arterial pressure 200 110 mm Hg. Leukocytosis 12,000, erythrocyte sedimentation 42 mm per hour. No signs of myocardial infarction on electrocardiogram. X-ray examination of the chest revealed an aneurysm in the ascending aorta. Two days later the patient's condition took a sharp turn for the worse, with dyspnoea, the patient lost consciousness and died on the third day after his admission to the hospital.

The autopsy revealed a dissecting aneurysm extending from the transverse part of the aorta to the iliac arteries. The rupture of the aorta occurred at the level of deviation of the sinistral subclavial artery and spread distally to the point of deviation of the iliac arteries. Orifices of the intercostal and lumbar arteries were included in the rupture. A microscopic examination revealed distinct symptoms of atherosclerosis of the blood vessels. A patch of softening was found in the spinal cord, at the level of the mid. thoracic segments. Numerous perivascular haemorrhages, diffused in the white and grey substance, were evident in the upper thoracic region of the spinal cord.

A similar case was described by M. V. Kochergin and E. I. Yeselevich who did not discover any distinct changes in the spinal cord.

In two cases of rupture of an aortic aneurysm described by L. G. Yerokhina, A. S. Ogurtsova and N. P. Mogilevchik, an acute progressive atonic paraplegia of the lower extremities began suddenly, accompanied by symptoms of collapse. A histological examination enabled the authors to find diffuse degenerative anoxaemic changes in the cerebral and cerebrospinal cells and disintegration of myelin in the marginal zone of the lower thoracic section of the spinal cord.

Lesions of the central and peripheric nervous system in the case of aortic rupture are caused by disturbances in the blood supply and ischemic syndromes:

1. Ischemic necrosis of peripheral nerves. The clinical picture reveals a paralysis of the extremities with anaesthesia and disappearance of tendon reflexes. The extremity is usually cold to the touch, and its pulse is not palpable.

2. Ischemic necrosis of the spinal cord which is characterised by a flaccid paralysis of the lower extremities

with conductive sensorial disturbances and urinary retention. Cerebrospinal lesions are caused by clottage of intercostal and lumbar arteries.

3. Ischemic necrosis of the cerebrum which brings on stupor or coma with hemiplegia in consequence of the extension of the haemorrhage to the a. carotis, or a. innominata due to disturbances of the blood flow to the basins of the middle and anterior cerebral artery.

Cerebral lesions do not always depend upon mechanical clottage of the arteries branching out of the aortic arch. Loss of consciousness, convulsions and hemiplegia appear in some cases without blocks of the arteries which supply blood to the brain. In similar cases cerebral symptoms are explained by shock and sudden fall of arterial pressure.

Aortic thrombosis also brings on paraplegia accompanied by pain in the extremities, shoulder blades, along the spinal column, and in the perineum. L. G. Yerokhina, A. S. Ogurtsova and N. P. Mogilevchik reported two cases of aortic thrombosis when the patients felt no pain at all. The collapse was accompanied by sudden paraplegia with sphincteral disturbances and the disappearance of pulsation in the femoral arteries.

In most cases, unruptured aortic aneurysms evoke no pain, but sometimes the pain may be very severe. That is especially true in cases when an aneurysm is localised in the aortic arch and is extending upwards. In such cases pain is caused by pressure upon intercostal nerves and parietal pleura.

I. A. Vilk, S. G. Moiseyev and others emphasise that in cases of rupture in the aortic arch pain appears in the region of the heart, behind the sternum, radiating into the shoulder blade and along the spinal column. In the opinion of L. G. Yerokhina, A. S. Ogurtsova and N. P. Mogilevchik, the level of conductive sensorial disturbances may to a certain degree serve as a basis for locating the thrombus in the aorta.

HYPERTENSIVE DISEASE

According to existing concepts, the hypertensive disease is a neurogenic disorder conditioned by traumatism and overstrain of the higher nervous activity. In compliance with the views of the Soviet therapeutic school (G. F. Lang, A. L. Myasnikov), the development of the hypertensive disease is caused by primary disturbances of the cortical regulation of the blood pressure mechanisms. Disturbances of the higher nervous activity which lie at the basis of the hypertensive disease are considered by G. F. Lang a neurosis characterised by pathological inertia or inert excitation in the sphere of higher regulation of the blood pressure. Consequently, the disease is a neurosis in its primary stages. The disturbances in the function of the vascular pressure system associated with it cause the appearance of angiospastic symptoms followed by organic changes in the blood vessels. Both the former and the latter lead in their turn to secondary cerebral lesions. It should, however, be borne in mind that the same nervous reactions may be observed in symptomatic hypertension caused by nephritis, Cushing's syndrome, pheochromocytoma, or coarctation of the aorta.

Nervous Symptoms in the Initial Phases of the Hypertensive Disease. The decisive factors in the mechanism of pathological changes, which lead, subsequently, to anatomical changes, are disturbances of innervation which cause spastic contractions of the minor arteries. This spasm may call forth nervous symptoms as early as in the initial stages of the disease. By collecting anamnestic information it may be possible to establish that attacks of migraine and of nervous asthenia, giddiness and semiconsciousness after taking wine, or on a sultry day, were observed long before the appearance of pronounced symptoms of the disease. Some patients complain of a feeling of uncomfort in crowded premises, or during sharp fluctuations in atmospheric pressure. Excessive vegetative

reactions are often produced even by slight emotional stimulations.

Nervous symptoms which often appear in the initial stage of the hypertensive disease compel some of the patients to consult a doctor before symptoms of cardiac or vascular insufficiency have appeared. Most frequent among these symptoms are headaches which may be the patient's only complaint.

The nature of hypertensive headaches may differ, and their localisation is equally varied. Most frequently they are localised in the occipital region, but may also be felt in the frontal, sincipital, or temporal regions. They may be unilateral, or bilateral. Diffuse headaches are rarer than local headaches. There are "typical" headaches which begin early in the morning, or at night. In the next few hours the headache disappears gradually, recurring every morning and becoming more intense with the progress of the disease. This type of headaches may in some cases disappear for many months, only to reappear again. Along with these "typical" headaches, there are headaches of another character expressed in attacks associated with fatigue, emotional strain, or insomnia. In more advanced stages of the hypertensive disease headaches may become constant; in some cases they are accompanied by vomiting. Recent investigations have shown that the leading role in the pathogenesis of headaches belongs to stimuli of the cranial vasoreceptors (A. M. Grinstein, I. Y. Razdolsky and H. G. Wolff).

Numerous observations made during operations have revealed that, like the cerebral substance itself, the pial membranes and vasoplexuses of the brain are insensitive to pain. A rise in intracranial pressure by itself cannot cause headaches, because it may sometimes be observed that a rapid fall in intracranial pressure produced by a lumbar puncture may condition a temporary intensification of headaches. All the tissues covering the cranium, and the cranial arteries especially, are more or less sensitive to pain. Most sensitive to pain among the intracranial systems are the venous sinuses, the veins entering them, a part of the dura mater at the

base of the brain and the arteries of the dura mater. The cranium, the cerebral substance, the greater part of the dura mater, the pial membranes and vascular plexuses are insensitive to pain.

The pathogenesis of hypertensive headaches resembles that of migraine. Changes in the intensity of headaches in migraine and in the hypertensive disease depend upon the fluctuations in the pulsation of the cranial arteries, mainly, in the branches of the external carotid artery. The factors which reduce the pulsation rate relieve the intensity of the headaches. Thus, ergotamine relieves or stops the headaches by reducing the pulsation rate in the cranial arteries. Reduction of the pulsation rate in the temporal artery by compressing it has been known to weaken headaches on the corresponding side in many cases. Headaches may be stopped by ligation of the temporal or middle meningeal artery (I. Y. Razdolsky, L. V. Perelman, L. T. Chlenov and L. M. Sherman).

A. M. Grinstein distinguishes three types of headaches whose localisation depends upon which of the vascular receptors are being stimulated. Pain in the region of the eyeballs and behind them, at the radix nasi and in the lower part of the forehead are produced by "distonia" of the ophthalmic artery. In such cases, sharp pain is conditioned by pressing at the internal angle of the upper edge of the eye socket upon the adjoining frontal artery, the terminal branch of the ophthalmic artery. The second type corresponds to the location of the middle meningeal artery. Its dilatation produces pain in the hairy part of the head extending up to the external occipital protuberance. The third type corresponds to the topographical distribution of the branches of the vertebral artery. Pain is felt in the occipital region and along the posterior surface of the neck. A. A. Kedrov and A. I. Naumenko believe that headaches are produced by stimulation of the receptors of the dura mater sinuses, rather than those of the arteries.

The level of arterial pressure alone does not influence the appearance and intensity of headaches. Out of 400 pa-

tients admitted to the hospital for nervous diseases with cerebrovascular accidents 225 never complained of headaches before. In fifty cases, where headaches were the leading symptom, the average pressure was the same as in 50 other patients who had never complained of headaches. Consequently, no direct correlation between the level of arterial pressure and headaches has been established. It should, nevertheless, be noted that in many cases headaches appear after a rise in blood pressure. This leads to the conclusion that a cranial artery while being slightly relaxed does not distend so much as to cause headaches if the arterial pressure is low; but when pressure rises the artery distends to a greater degree and may evoke headaches.

As already mentioned before, headaches frequently are the only symptom in the initial stage of the hypertensive disease. Its symptomatic treatment is a difficult task. What is necessary in the first place is general treatment of the hypertensive disease, but it is not the purpose of this book to discuss it. Pyramidon with caffeine and codeine may be prescribed for relieving headaches. L. F. Dmitrenko recommends small doses of caffeine (0.02-0.03 g) until headaches cease. Sodium amytal may sometimes be useful to take for the night. Some patients find relief after the inhalation of oxygen for several minutes. In other cases, a favourable effect may be produced by nicotinic acid. Reserpine has not only an antihypertensive effect, but also a sedative action. In many cases a long-term administration of reserpine reduces the intensity and frequency of headaches.

For relieving morning headaches it may be recommended to raise the head end of the bed by 30-40 cm. The patient should sleep in a cool, well ventilated room.

Great significance is attached to psychogenic factors. The patient should be comforted, and everything should be done to remove irritating and depressing factors, as well as excessive strain. In some cases a month's rest far

away from the usual irritating factors stops headaches for a long time.

In more advanced forms of the hypertensive disease, or in the presence of symptoms of cerebral oedema, leeches may be applied over the mastoidea, and intravenal, or intramuscular injections of magnesium sulfate may be recommended. A lumbar puncture may be prescribed only in cases where symptoms of high intracranial pressure are evident. Our experience has shown that ordinarily a lumbar puncture brings no substantial relief.

Giddiness in the hypertensive disease is rarely of the nature of the Menière symptoms with vertigo, as it is observed in an a. auditiva interna spasm. It is expressed most frequently in a sudden feeling of weakness and dimness of vision so that the patient is often compelled to lean against a wall, or to sit down. This is aggravated by a feeling of heaviness in the head, and in some cases also by brief dimness of consciousness. A headache, which is indicative of a disturbance in the tone of the cranial arteries, is prognostically not as threatening a symptom as giddiness which is indicative of functional insufficiency of the cerebral vessels. In some cases giddiness appears during a change to a supine position; that is explained by cerebral hyperaemia. A mild temporary stasis in the veins and a rise in venous pressure is observed ordinarily in healthy people in a supine position. Due to the reflex contraction of the cerebral arterioles, the blood flow through the capillary network is increased, thus equalising this stasis. The altered cerebral vessels of a person suffering from the hypertensive disease are incapable of such rapid compensatory change. Hence the transient symptoms in the form of giddiness, tinnitus aurium and hyperaemia. The auricular and cranial tinnitus in the hypertensive disease may be both transient and constant.

Studying vegetative disturbances in patients suffering from hypertensive disease, Z. Y. Svetnik and G. A. Safonov took special note of hyperaemia, with a deep red-

dening of the neck and chest, and in some cases of the whole body, attended by a feeling of fever and other uncomfortable sensations. In other cases, on the contrary, there is a chilly sensation in the extremities and marbling of the skin of the extremities and body. A peculiar syndrome may sometimes be observed especially in young women suffering from angioneurosis: red blotches appear on the face, on the neck and body, the eyes fill with tears, the body is covered with perspiration, the extremities grow chilly, the pulse quickens and the arterial pressure rises. The attack may come on spontaneously, or in a state of emotional excitement. This syndrome bears some resemblance to diencephalic epilepsy. G. F. Lang observed it in a very distinct form in patients suffering from the hypertensive disease.

An important place in the picture of the hypertensive disease belongs to pseudoneurasthenic symptoms; fatigability, mild depressions and their expressed forms, complete exhaustion, a feeling of discomfort, attacks of fear, fear of company and conversation and changeability of mood. The mentioned symptoms create a vicious circle. A rise in arterial pressure makes the patient more excitable, irritable and produces other neurasthenic symptoms which, in their turn, tend to raise arterial pressure. Insomnia is another factor of this type, depriving the patient of the necessary rest.

On the basis of a great number of clinical observations N. I. Ozeretsky distinguishes the following psychopathological syndromes in the hypertensive disease: 1) the cerebroasthenic syndrome, including mental depression with a shade of fear, memory failure, reduction or loss of working efficiency; 2) the agitative-depressive syndrome, characterised primarily by depression, anxiety, fear, and in some cases, by an ecstatic state. A most frequently observed syndrome, according to N. I. Ozeretsky, is psychic asthenia expressed in diffidence, mistrustfulness or anxiety. In other cases emotional instability, high irritability and

irrascibility are observed. Paranoid and pseudoparalytic syndromes are observed much rarer.

V. A. Gilyarovsky and V. F. Zelenin distinguish psychic disturbances in the various stages of the process. In their opinion, an active character, and rarer—an overanxious one—is characteristic of the premorbid state; neurasthenic symptoms with preserved activity, emotional instability and keen perceptions—for the period of unstable rises in pressure; episodic changes in the psychic tone, high fatigability in the period of a stable rise of pressure.

The distinctions mentioned above are in their greater part conditional. Quite often more or less emphasised premorbid traits of character can be related to the psychic disturbances in the hypertensive disease. In some cases it is a question of the patient's reaction to his disorder, in others some scientists are inclined to consider adjoining organic changes in the cerebrum as expressions of the "hypertonic's psychology". Y. S. Averbukh believes that in the case of slow development of the vasocerebral process, pseudoneurotic conditions may arise as a result of the expression of the specific nature of the premorbid personality. In some cases, disinhibition of psychopathic traits which has been compensated for many years may be revealed.

On the basis of his own observations N. K. Bogolepov reached the conclusion that the psychic changes in persons suffering from the hypertensive disease can be classified as 1) changes in character tending towards greater irritability, excitability and irrascibility combined with asthenia (the patients grow weak, uncertain of themselves and are easily susceptible to fatigue); 2) disturbances of the emotional sphere with a state of depression, uneasiness and anxiety; 3) disturbances of formal abilities: retardation of psychic processes, difficulty in changing psychic moods, memory failure and poor attention. G. F. Lang notes that N. K. Bogolepov's description reveals features which are indicative of a weak type of higher nervous activity with

inert psychic processes and high emotional excitability. G. F. Lang, however, is inclined to doubt to what extent this state may be a consequence or a cause of disease.

The types of higher nervous activity in the hypertensive disease have been studied by L. B. Gakkel, V. V. Yakovleva and B. I. Stozharov. L. B. Gakkel has found that persons with a weak type of higher nervous activity predominate among hypertonics. This conclusion is rather unexpected, inasmuch as energetic, active and resourceful people are often found among hypertonics. V. V. Yakovleva and B. I. Stozharov found that among the patients examined by them 46 per cent had a strong type of higher nervous activity: out of 142 patients 52 had a strong, balanced type, 77—a weak type and 13—a highly excitable type. A study of conditioned reflex activity was based on the dynamic method with verbal reinforcement recommended by A. G. Ivanov-Smolensky. The data obtained requires a further study.

Rise in Intracranial Pressure. Patients with a high intracranial pressure constitute a special group. They often show signs of hepatorenal and cardiovascular insufficiency. Intracranial pressure may develop slowly, but often it rises rapidly in the case of malignant hypertension. Its symptoms are headaches, vomiting and bradycardia. Meningeal symptoms may also appear later. All these developments, combined with changes in the eyeground, create the picture of a pseudotumour. Nevertheless, cases are known when a considerable increase in intracranial pressure has taken place without any clinical symptoms.

Changes in the eyeground represent the earliest and most frequent symptom of a rise in intracranial pressure. The finding of these changes in malignant hypertension is of great diagnostic and prognostic value. Changes in the eyeground may be of two types: 1) neuroretinitis, just as in the case of persons suffering from renal disorders; 2) stasis with dilatation of the veins and different variations of papilloedema, beginning with occult pericapillary stasis without

exudation and ending with extreme dilatation of the vessels with considerable exudation and radial foci of blood effusions. In some cases, neuroretinitis combined with papilloedema have been observed. The described changes may occur in the early stages when lesions of the kidneys and heart are insignificant.

In most patients of this group changes in the eyeground are combined with hypertension of the cerebrospinal fluid (up to 200-500 mm), and in some cases also with albumino-cytologic dissociation. These cases may be quite difficult for differential diagnosis and for distinguishing them from a cerebral tumour, as the following observation will show.

Patient B., 29 years of age, had never complained about her health before. Headaches appeared in June 1939, and impairment of vision was observed a month later, first in the left eye and then in the right eye. An opthalmologist found a papillary stasis, and on October 23, 1939 the patient was placed in the clinic of the Neurosurgical Institute with the diagnosis of a cerebral tumour. This diagnosis was rejected and the patient was transferred to the Botkin Hospital.

The mucous membrane of the lips, the skin of the face and ears —cyanotic. Heart boundaries slightly dilated to the left, diameter 11.5 cm, vascular bundle 4 cm. Pulse rate 100 per minute. Accentuation of the second sound at the aorta. Arterial pressure 175 130 mm Hg. Lungs normal. Liver and spleen not palpable. No organic nervous symptoms with the exception of a hint at Babinski's sign on the left. Boundaries of the optic disks more obscured on the left. Veins dilatated, their orifices uneven, a node of atrophy, the trace of a past haemorrhage, on the left, in the region of the macula lutea. Fresh haemorrhages visible in both eyegrounds. Visual acuity of both eyes 0.09. Albumin in urine 0.45 ‰; no other deviations from normal. Blood: adrenalin 0.17 mg%, creatinine 2.2%, sugar and chlorine normal. Wassermann reaction negative. Cerebrospinal fluid: pressure 290 mm, albumin 0.39%, cytosis 0.

Discharged a month later in considerably improved condition.

Subsequent medical observation confirmed that the diagnosis of hypertensive disease was correct.

A rise in intracranial pressure in patients suffering from the hypertensive disease is not directly connected with a higher arterial pressure, inasmuch as in most cases it

remains normal although the arterial pressure may be high. In some cases an increase in intracranial pressure is due to high venous pressure associated with disorders of heart compensation.

A. I. Zlatoverov, Alajouanine and Thurel are inclined to consider venous hypertension a basic cause of high intracranial pressure, but I. I. Blashko's investigations have shown that in many patients with high intracranial pressure the venous pressure remains normal. An essential role is apparently played in these cases by toxic factors, by disturbances in chloride and water metabolism. It is as yet impossible to define the role of each of these factors. Clinical observations have shown that azotemia alone does not produce a high intracranial pressure. Evidently, the retention of chlorides may be a more important factor here.

Azotemia, without causing a high intracranial pressure, may often be a symptom of kidney lesions calling forth disturbances in the metabolism of chlorides and water. Therapeutic measures (proper regimen, diet and treatment) may in some cases lead to a noticeable decline in intracranial pressure and thus confirm the role of toxic factors in its increase. In some cases, proper treatment increases diuresis, chloraemia and azotemia disappear, intracranial pressure reduces to normal, while arterial and venous tension remain unchanged.

Hypertensive Crisis and Acute Cerebral Oedema. In the clinic of the hypertensive disease a prominent place is occupied by intercurrent relapses expressed in headaches, giddiness with nausea and often with vomiting, and marked weakness. Dimming of consciousness is observed in some cases. This is very often accompanied by symptoms of meningeal irritation, such as occipital rigidity, Kernig's and Brudzinski's signs. In some cases in the terminal stage symptoms of focal lesions of the brain expressed in transient paralysis, aphasia, hemianopsia and sensorial disturbances may be observed. The latter occur in some cases

also in the absence of severe headaches, vomiting, etc. These conditions are diagnosed as a cerebral crisis or dynamic disturbance of cerebral blood circulation. They are always accompanied by greater or smaller rises in arterial pressure.

In some cases this crisis is expressed in headaches and vomiting only. N. V. Konovalov distinguishes two types of cerebral crises. The first is marked by headaches, a feeling of heaviness in the head, giddiness, vomiting and marked general weakness. Consciousness remains clear, the patients are merely depressed and absent-minded. The second type is characterised by a confusional state or the loss of consciousness.

Symptoms of cerebral oedema are present in all cases of severe crisis. Clouding of consciousness may be more or less deep, a soporous state may pass into a coma. Positive Kernig's and Brudzinski's signs are revealed very rarely; rigidity of the occipital muscles, high pressure of the cerebrospinal fluid and slow pulse rate create the picture of a pseudotumour.

Changes in the eyeground are quite frequent. We have already mentioned acute or subacute amblyopia, or amaurosis observed in some cases. Objective signs are oedema in the eyeground and protruding optic papilla with blood effusions into the retina, and sometimes also with constriction of the arterioles.

The following case history may serve as an illustration.

Patient S., age 60, did not remember having been ill in the past. Headaches and giddiness appeared in the morning of October 31, 1946. A few hours later headaches became much more severe, and a clouding of consciousness followed. On the same day the patient was taken to the hospital. The patient was inert, drowsy, with periodical motor excitation. Hyperaemic face. Occipital rigidity, Kernig's and Brudzinski's signs. Cranial nerves normal. No signs of focal lesions of the central nervous system. Eyeground normal. Boundaries of the heart slightly dilated, tone dull. Pulse rate 80 per minute. Arterial pressure 180/100 mm Hg, cerebrospinal fluid colourless, albumin 1.32 ‰, cytosis 1, pressure 250 mm. Wassermann's

reaction in blood and cerebrospinal fluid negative. Urine unchanged. Marked improvement in the patient's condition a few days later. Meningeal symptoms disappeared. Discharged on November 26 in good condition. Arterial pressure 130 80 mm Hg.

We have observed a similar picture in other patients suffering from the hypertensive disease. The syndrome develops acutely, with a soporous state. Psychomotor excitation, and, in rarer cases, epileptic seizures are observed. Distinct meningeal symptoms appear in the form of occipital rigidity and Kernig's and Brudzinski's signs. Symptoms of focal lesions of the cerebrum are not found ordinarily. Signs of hemiparesis, or pyramidal symptoms are observed in some cases. The cerebrospinal fluid is colourless, transparent, its pressure rising to 250-600 mm, the content of albumin in 50 per cent of cases increased (0.45-1.6‰), cytosis normal. All the symptoms ordinarily disappear within 3-10 days. The state described may recur, or alternate with other cerebral lesions observed in the hypertensive disease. In malignant cases death may occur with symptoms of decline in heart functioning, respiration disturbances of the Cheyne-Stokes type, or oedema of the lungs.

Patient T., age 53. Considered himself ill since 1941, when headaches first appeared. Arterial pressure at that time was 160/100 mm Hg. In December 1946, was brought to a hospital of internal diseases with severe headaches accompanied by vomiting. Arterial pressure at the time of admission to the hospital 220/130 mm Hg. Discharged two weeks later in a considerably improved condition with arterial pressure of 160/100 mm Hg. His condition deteriorated two months later: a confusional state of consciousness was observed, headaches and vomiting appeared. The patient was stunned, adynamic. Occipital rigidity, Kernig's and Brudzinski's signs. No symptoms of focal lesions of the brain. Arterial pressure 250/140 mm Hg. Pressure of cerebrospinal fluid 260 mm, albumin 1.62‰, cytosis 1. Urine gravity 1,030, albumin 0.06‰. Several days later the condition grew worse again. Respiration rhythm upset. The patient lapsed into a soporous state, answered questions after long pauses, in whispers. Grasp reflex appeared on the right. The neurological symptomatology bore a close resemblance to the picture of a pseudotumour. The patient died.

Pathological diagnosis: Hypertensive disease, pronounced hypertrophy of the heart (of the left ventricle especially), marked general atherosclerosis with predominant lesion of coronary arteries of the heart and cerebral vessels, sharp oedema of the brain, small cysts in the subcortical ganglia.

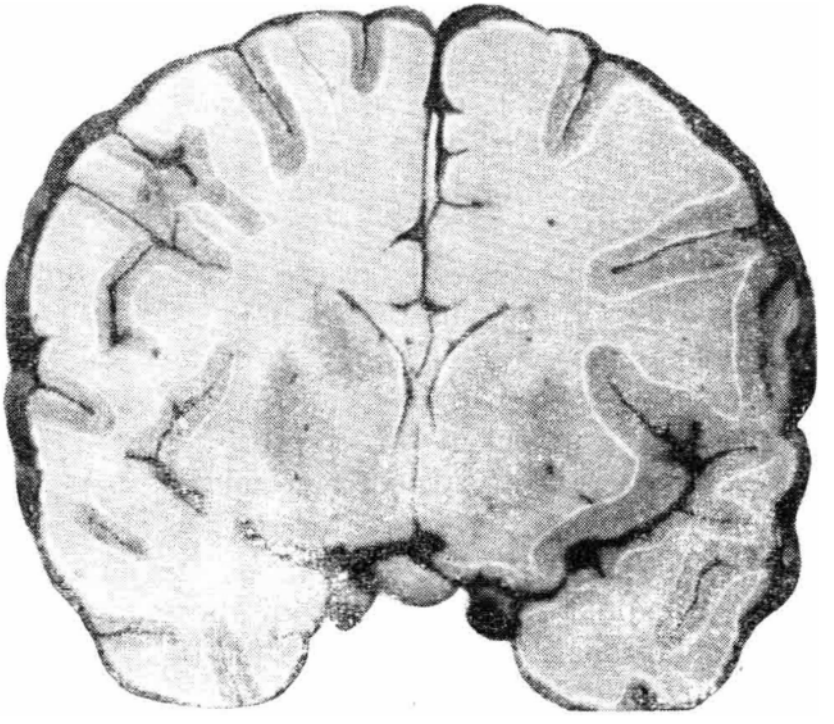

Fig. 5. Hypertensive disease. Acute cerebral oedema. Flattening of cerebral convolutions and compression of the ventricles

Histopathological examination: Subarachnoid space distended. Veins and capillary vessels dilatated. Severe dilatation of perivascular spaces. Staining according to Van Gieson's method revealed amorphous rose-coloured masses in the Virchow-Robin spaces. Nodules of erythrodiapedesis and leukodiapedesis scattered around. Changes most pronounced in the region of the subcortical ganglia, around the ventricles and the sylviduct.

During the examination of the brain attention was attracted by the increased volume of the cerebral hemispheres and flattening of the cerebral convolutions. Arterial walls thickened and hyalinised. Absence of distinct boundary between the white and grey substances. Brain more rose-coloured than normally, ventricles contracted (Fig. 5).

The pathogenesis of the cerebral crisis is as yet inadequately clear and is still the subject of many disputes. The first to describe vascular crises, Pal distinguished general and local crises. He believed that general vascular crises were characterised by rapid increase in the general arterial pressure resulting from spastic contractions of the vessels of the systemic circulation, while passive hyperaemia and a rise in intracranial pressure took place in the cerebrum. This type of mechanism of a cerebral crisis is easily explained by acute oedema of the brain, rather than by local vascular spasm.

It has long been noticed that there is some resemblance between a cerebral crisis and ecclamptic uraemia. Volhard also attached decisive significance to cerebral oedema as a factor responsible for the pathogenesis of this disease and considered it a result of cerebrovascular spasms. Volhard believed that in a vascular crisis the arterioles of the cerebrum contract to a greater degree than in other organs.

Indicative against the hypothesis of the leading role of cerebrovascular spasms is the fact that the arterioles of the cerebrum not only do not contract more than the other arterioles, but, on the contrary, they are much less susceptible to contraction. That is proved by the following data. Cerebral vessels possess a much thinner muscular wall than arteries of the same size in other organs. The medial coat of the cerebral arterioles is composed in the main of collagenic fibers, while the muscular fibers are scarce and in some places they are absent altogether. Experimental investigations conducted on animals have shown that cerebral arteries contract to a much lesser degree than the cutaneous arteries. Adrenalin applied directly to cerebral arteries contracts them very little, but intravenal injection of adrenalin raises the blood pressure owing to the contraction of the peripheral arteries, while the pial arteries increase in diameter.

On the basis of numerous experiments it has been found that when the cervical sympathic ganglia are stimulated contraction is observed only in the cerebral vessels with a diameter above 50 microns, the contraction amounting to 8-10 per cent of the original orifice, while the cutaneous vessel contracts to a ten times greater degree. No contraction is observed in the smaller arterioles and in the capillaries. It has been shown that the cerebral vessels are not involved in the vasoconstriction process caused by a fall in pressure in the carotid sinus. Consequently, cerebral arteries react very weakly or do not react at all to vasoconstricting agents.

Fischberg, who also adhered to this viewpoint, subsequently abandoned it. He believes that under the action of impulses which lead to strong contraction of arterioles in the organism, the cerebral capillaries, on the contrary, tend to dilatate. Evidently, pressor substances which cause spastic contractions of peripheral vessels, exert an antagonistic action on the cerebral vessels, conditioning their dilatation. This antagonistic action on the peripheral and cerebral vessels has been proved for caffeine. Cerebral oedema is observed not only in vascular diseases. During operations on the posterior cranial fossa neurosurgeons noted a sharp rise in arterial pressure followed by dilatation of the cerebral vessels of all sizes and by cerebral oedema. Changes in the chemical composition of the blood may also cause dilatation of the blood vessels by acting upon the vasoreceptors. An increase in the content of carbon dioxide in the blood accounts for dilatation of the cerebral vessels. Many poisons (nitrites, alcohol) and gases (carbon monoxide, hydrogen) exert the same action. An acute cerebral oedema leads to an active dilatation of the vessels with haemostasis, increased permeability of the capillaries and exudation of liquid and, subsequently, of albumin from the cerebral vessels.

I. V. Davydovsky and A. N. Koltover believe that paralysis of the walls of the minor cerebral vessels calls forth

a severe increase of the permeability of the vessel walls and in their saturation with albumin: plasmorrhagia. Disturbance of vasopermeability causes perivascular oedema of the cerebral substance.

G. F. Lang pointed out that there were "practically no direct observations of cerebrovascular spasm, nor any observations of their dilatation preceding a cerebral oedema". However, he found proof in support of the tonic spasm in the arteriole constrictions and spasm in the eye-ground observed in the hypertensive disease. Consequently, G. F. Lang considered more correct the concept of angiospastic genesis of cerebral oedema "in consequence of sharp rise in the tonic contraction of the cerebral arterioles and the state of peristasis and stasis caused by that". A differential diagnosis between an acute cerebral oedema and cerebral apoplexy in the hypertensive disease presents no difficulty. In the latter case hemiplegia is always in the foreground; in the case of acute oedema there are no focal disturbances, the entire syndrome being expressed in general cerebral and meningeal symptoms. It is more difficult to distinguish between cerebral oedema and a hypertensive subarachnoid haemorrhage. In some of our patients the clinical picture bore complete resemblance to a subarachnoid haemorrhage, and only when a non-haemorrhagic colourless transparent cerebrospinal fluid was removed following a puncture was it possible to reject that diagnosis.

In the treatment of a hypertensive crisis measures should be taken to reduce arterial pressure, prevent a decline in cardiac activity and relieve intracranial pressure.

Hypertonic solutions are used for relieving cerebral oedema, and, primarily, magnesium sulfate (a 25% solution, administered intravenously or intramuscularly in doses of 10-20 ml). Magnesium sulfate is used not only as a means of reducing intracranial pressure, but also as a sedative. In cases where magnesium sulfate has a depressing action on respiration, it should be prescribed together with cal-

cium gluconate. In many cases headaches are instantly relieved by a lumbar puncture. But when a puncture is prescribed, all precautions should be taken, because cerebral oedema may cause displacement of the cerebellum and wedge it into the occipital fossa. Gangliablocking and sympatholytic agents, hexamethonium and apressin, have lately been recommended for a rapid decline of arterial pressure. But these drugs should not be prescribed for elderly patients and in cases when symptoms of atherosclerosis of the cerebral vessels are evident, inasmuch as a rapid fall in arterial pressure may cause cerebral softening in consequence of an insufficient blood supply to the brain. In such cases it would be better to apply Rauwolfia derivatives (reserpine, serpasil).

According to N. A. Ratner, E. A. Denisova and N. A. Smazhnova, intravenous or intramuscular administration of dibazolum leads to a rapid fall in arterial pressure, relieves headaches, vomiting, nausea and even cerebrofocal symptoms.

In the case of a hypertensive cerebral crisis phlebotomy from the ulnar vein does not affect a cerebral oedema, while an attempt to discharge 400 ml or more blood for the purpose of bringing about a substantial reduction in pressure may retard the blood flow and provoke a stroke.

Transitory and Minor Focal Lesions of the Cerebrum. Transitory focal symptoms of cerebral lesions, such as different types of paralysis, paresis, attacks of aphasia, haemianaesthesia, or haemianopsia, are observed in the hypertensive disease much more often than acute cerebral oedema. They appear suddenly and disappear within a few minutes, hours, or days. In some cases these disturbances recur again and again; the first attacks may leave no consequences, while protracted disturbances in the form of paresis and sensorial disorders remain after subsequent attacks. Development of the pseudobulbar syndrome is observed in some cases: choking with food, dysarthria, forcible crying and laughter.

G. F. Lang believes that combinations of transitory disturbances in cerebral blood circulation with transitory amaurosis of one or both eyes and obviously angiospastic symptoms in the extremities "give the right for assuming precisely an angiospastic genesis of these symptoms of hypertensive disease". In G. F. Lang's opinion, repeated relapses and identical types of these symptoms speak in favour of this point of view.

It should nevertheless be noted that there is no convincing proof of spastic contractions of the cerebral vessels in the case of minor focal lesions. At any rate, at the patient's bedside it is extremely difficult to distinguish between symptoms produced by minor focal lesions and symptoms produced by spasm or stasis only. Attention to this is directed by G. F. Lang when he writes: "It is hard to tell which of the disturbances of central nervous functions are caused by angiospasm and which by thrombosis of the minor arteries, or arterioles, or by minor haemorrhages."

In some cases of hypertensive diseases disturbances of the cerebral circulation are accompanied by a fall rather than by a rise in arterial pressure. On the basis of histological examinations of the brain of people who died of the hypertensive disease, K. G. Volkova arrived at the conclusion that in the presence of atherosclerosis a fall in arterial pressure may produce acute anaemia with transient disintegration of some functions.

Increasing symptoms of arteriosclerosis and arteriolonecrosis may lead to more or less permanent disturbances in the cerebral vessels as a consequence of the exclusion of a part of the capillary network. Evidently, various mechanisms may be responsible for the origin of transitory disturbances in cerebral circulation.

Cerebral Haemorrhage. A haemorrhage into the brain is one of the most frequent consequences of the hypertensive disease. Out of 754 patients with hypertensive diseases observed by Pal, 249 died, and 140 of these deaths

were caused by cerebral haemorrhages. We have found the hypertensive disease in 90 per cent of the cases of cerebral haemorrhages at post-mortem examinations. Reference is often made to a type which is most susceptible to cerebrovascular accidents. Emphasis has been laid on the presence of minor vascular changes in the cutanea, haemangiomas, the tendency towards nasal haemorrhages, rapid vasomotor reactions and symptoms of adiposogenital dystrophy. All these symptoms, usually encountered in the hypertensive disease, are hardly of any prognostic value in relation to an accident. An examination of the heart and kidneys gives a satisfactory idea of the state of the renal and coronary vessels, but there is as yet no method which would reflect the condition of cerebral circulation. Only some clinical facts furnish the ground for the assumption that a patient is threatened by a cerebral haemorrhage.

Cases have been observed when a cerebrovascular accident was not preceded by any nervous symptoms. In most cases, however, severe headaches, giddiness and faintings, brief attacks of aphasia, paresis and paresthesis, blood effusions into the retina and frequent nasal haemorrhages have been observed. The combination of several of these symptoms is an unfavourable sign indicative of a possible cerebrovascular accident. The latter is observed most frequently in cases of malignant hypertension, especially in young people in whom hypertension develops within a year or two, often ending in death from cerebrovascular accident. Neuroretinitis is found early in such cases of the hypertensive disease. Although the patient should be told that the blood pressure alone is not yet indicative of the gravity of the disease, it nevertheless may to a certain degree serve as a prognostic criterion. The number of deaths occurring when the blood pressure is above 200/120 mm Hg is doubly greater than when the pressure is below 180/110 mm Hg. Not only the usual pressure is important, but also the maximum attained as the result of

pressor stimulation. Many accidents occur in the process of this increase. In addition to emotional tension, attacks of increased pressure may be provoked by physical overexertion, exposure to cold, alcoholic intoxication, in some cases by fits of coughing, defecation and coition. However, it is not the purpose of this book to describe the clinical picture of cerebrovascular accidents.

THROMBOANGIITIS OBLITERANS

The disease was first described by Winiwarter, in 1879, as an independent disorder, its characteristic feature being clottage of the arteries in the lower extremities as the result of a chronic proliferative process concomitant with the expansion of intima cells. Buerger (1908, 1924) found that the thrombotic process affects not only the arteries of the extremities, but also the veins, and named the disease thromboangiitis obliterans. Investigations conducted by M. I. Khvilivitskaya, D. I. Panchenko, S. I. Shakhnovich, Z. L. Lurye, Jäger and others have shown that the disease may affect not only the vessels of the extremities, but also those of the viscera and the brain. According to information given by different authors, cerebral vessels are affected in 2-20 per cent of the cases of thromboangiitis obliterans.

The disease usually begins with intermittent claudication, pain in the legs and weakness, followed by the absence of pulsation on the arteries of the legs and migrating phlebites. It is much more frequent among men than among women. Cerebral vessels may be affected simultaneously with the vessels of the extremities, as well as in the absence of symptoms of lesions of the extremities.

As is known in the initial stage of the disease pallor and a symptom of cold feet appear periodically. Pulsation in the lower extremities may disappear and then reappear again. Cerebral symptoms also bear a transient character in the early stage.

The clinical picture of cerebral lesions develops gradually, slowly, with remissions and exacerbations. Headaches, sometimes of the migraine type, are observed in the initial stage of the disease, along with a feeling of exhaustion, fatigue, reduced working efficiency, and, frequently, more characteristic symptoms such as intermittent claudication, stenocardia, or myocardial infarction become evident. Focal cerebral symptoms, mainly cortical, appear later, resembling the symptoms observed in atherosclerosis, or the vascular form of cerebral syphilis.

These symptoms are expressed in attacks of giddiness, transient haemianopsy, amaurosis, unilateral haemianaesthesia, mono- and hemiplegia, disturbances of speech and writing, general and Jacksonian epileptic seizures. Psychic symptoms expressed in confusional states, fits of excitation, depression, or apathy, are observed rarer. The abovementioned symptoms last for hours, days, or weeks, and then disappear rapidly, or gradually.

Transient focal disorders of the brain reappear after some time and then become permanent. The terminal stage of the disease brings on stable paralysis, aphasia, a pseudobulbar syndrome, forcible crying and laughter, confusional states and drowsiness. Psychic changes may reappear along with symptoms of focal lesions of the brain. Pictures of paranoid psychosis, mania and epileptic psychosis have been described by A. N. Popova and L. P. Demidova, M. M. Mirskaya and R. G. Golodets.

Our following observation may serve as an example.

Patient S., age 46, was admitted to the hospital on February 16, 1947 with complaints of weakness of the right extremities, giddiness and choking during eating. Had scarlet fever in childhood and typhus in 1918. In 1929, began to feel a slight giddiness in the morning. A month later was overtaken suddenly by sharp giddiness, ceased to distinguish objects underneath and on the side. The condition became worse two months later. Severe pain in the left leg along with redness of the toes appeared in 1935. The distal phalanges were amputated in the same year. In 1936, weakness appeared in the right wrist along with disturbances of speech ("understood

everything, but could not speak"). At the hospital the case was diagnosed as a tumour of the brain. The patient refused to undergo an operation. In August 1936, a feeling of weakness appeared in the left leg, and a loss of vision which the patient regained shortly thereafter. In February 1937, his vision was again impaired; he acquired a staggering gait, hiccoughs and difficulty in swallowing. Heart boundaries normal, tones clear. The accentuation of the second sound at the aorta. Blood pressure 110/70 mm Hg. Skin of the left foot cyanotic and spotted. The left foot colder than the right one. Pulsation of the left radial artery much weaker than that of the right. Pulse rate on the a. dorsalis pedis and a. tibialis postica not palpable on the left and barely distinguishable on the right.

Marked memory failure. The patient is easily excitable, irritable and lapses easily into an affected state. Amnestic aphasia. Reaction of the pupils to light and convergence normal. Rotatory nystagmus more pronounced when the eyes are moved rightward. The right nasolabial fold smoothened. In phonation the right half of the soft palate delayed. The patient chokes with solid food. Paresis of the right wrist and fingers. Tendon reflexes d > s. Abdominal reflexes are not elicited. Babinski's sign on the right. Hyposensitiveness to pain and heat on the right half of the face. Disturbance of muscular and joint sensitiveness in the fingers of the right hand. Venous vessels at the eyeground slightly wider than normal with an uneven orifice. Wassermann's reaction in the blood and cerebrospinal fluid negative.

Focal symptoms (monoparesis, aphasia, hemianopsia) are often caused, especially in the initial stage of the disease, by cerebral lesions which receive their blood supply from the distal cortical branches of the blood vessels. The cause of transient disturbances of cerebral circulation, which were explained by spastic contractions of the cerebral vessels, lies often in *thrombosis of the internal carotid artery.*

Contraction of the arteries, dilatation of the veins with punctuate haemorrhages are sometimes observed on the eyeground in the initial period; in far advanced stages of the disease atrophy of the optic nerves may develop after thrombosis of the central artery of the retina. The temperature usually remains normal, subfebrile temperature being observed on rare occasions. Blood pressure does not rise. Blood formula does not change. Accelerated erythro-

cyte sedimentation may be observed in some cases. Cerebrospinal fluid is normal, or with moderate albuminocytologic dissociation which may subsequently disappear.

A pneumoencephalographic examination in a far advanced stage of the disease may show symptoms of cortical atrophy expressed in dilatation of the ventricles and in considerable accumulation of air over the arch, especially in the region of the frontal lobes. Arteriography has in some cases made it possible to find occlusion of a large artery. Most of the cases of thrombosis of the internal carotid artery in thromboangiitis obliterans described recently have been discovered only through arteriographic examinations.

In most cases of cerebral thromboangiitis obliterans similar changes are discovered in the vessels of the extremities, heart, kidneys and pancreas. Not only small cortical branches of the arteries, but large arterial vessels at the base of the brain as well, are affected by the pathological process. It has lately been discovered that in many cases thromboangiitis is the cause of thrombosis of the internal carotid artery.

Lindenberg and Spatz examined cerebral vessels in 20 cases of thromboangiitis obliterans and found two basic types of lesions. The type most frequently observed is associated with distal cortical parts of the arteries. In such cases small cicatrixes in the shape of granular atrophies are evident in the cerebral cortex. A characteristic feature is the distribution of this atrophy in the border zone of the cerebral arteries. Cicatrixes begin in the region of the second frontal convolution and extend back along the edge of the arch towards the occipital pole. If the branches of the a. strio-lenticularis are affected, small nodules, most of them cicatrised, are found under the wall of the cerebral ventricles in the corpus striatum. Sections of the cortex which receive their blood supply from affected vessels may become softened. In the cases of the other type of pathological changes, more massive patches of softening may

be found in the zone of one or several arteries, chiefly in one hemisphere, mainly in the cerebral cortex.

Our following observation may serve as an illustration.

Patient N., age 48, was admitted to the hospital on August 31, 1950. No information was obtained about family and personal anamnesis. Considers himself ill since 1946, when headaches and vomiting appeared. No organic symptoms with the exception of high tendon reflexes were noticed in the hospital during the examination in December 1946. Dilatation of the veins with punctuate haemorrhages found in the eyeground. These symptoms gradually disappeared and the eyeground became normal a month later. Vomiting, severe headaches and a stunned state reappeared in the summer of 1949. Periodical headaches were observed later. On August 17, 1950 the patient suddenly lost consciousness. Headaches, vomiting and a severe deterioration of his general condition were observed in the days that followed.

Consciousness clouded. Sinistral ptosis. Eyeballs turned to the right. Sinistral hemiparesis. Babinski's and Oppenheim's signs on the left. Boundaries of the optic disks not quite distinct, venous vessels of the right eyeground wider than normal. Tension of cerebrospinal fluid 200 mm, albumin 0.3 ‰, cytosis 3. Wassermann's reaction in the blood and cerebrospinal fluid negative. The patient died on the fourth day after his admission to the hospital.

Post-mortem examination: Orifice of the left vertebral artery, at the point of its junction with the basiliar artery closed by dry red thrombotic masses. Cerebral cortex in slices narrow and rose-coloured. A patch of softening in the region of the internal capsule and the thalamus. The patch is not total, but composed of nodules and cysts of different sizes. In the same region of the other hemisphere the structural pattern is obliterated. Renal veins and arteries on the left closed by thrombotic masses.

Microscopic examination: Cardiac fibers of uneven thickness, with deposits of brown pigment. Walls of some of the cardiac arteries considerably thickened. Their orifices constricted to mere slits, the intima is wide with chaotically distributed proliferated endothelium. The median coat irregularly thickened. Small cellular infiltrations at the boundary with the adventitia. Large haemorrhagic regions under the endocardium. Renal fascicles repleted, some of them closed and hyalinic in appearance. Sections of granulation tissue in cortical interstice. Some arteries with markedly thickened wall and narrow orifice. Hyalinosis of the small vessels of the spleen. The orifice of one of the major branches of the splenic artery almost completely obliterated. Brown atrophy of the liver.

The obliterated left vertebral artery has slits lined with endothelium (an old thrombosis with restored lumen). In preparations taken from the cerebrum and cerebral trunk, attention is attracted by marked repletion of vessels with blood and vascular stasis. The latter is sharply pronounced in the thalamic regions, occipital cortex, less conspicuous in the frontal and temporal cortex and faintly expressed deep in the white substance and in the subcortical gan-

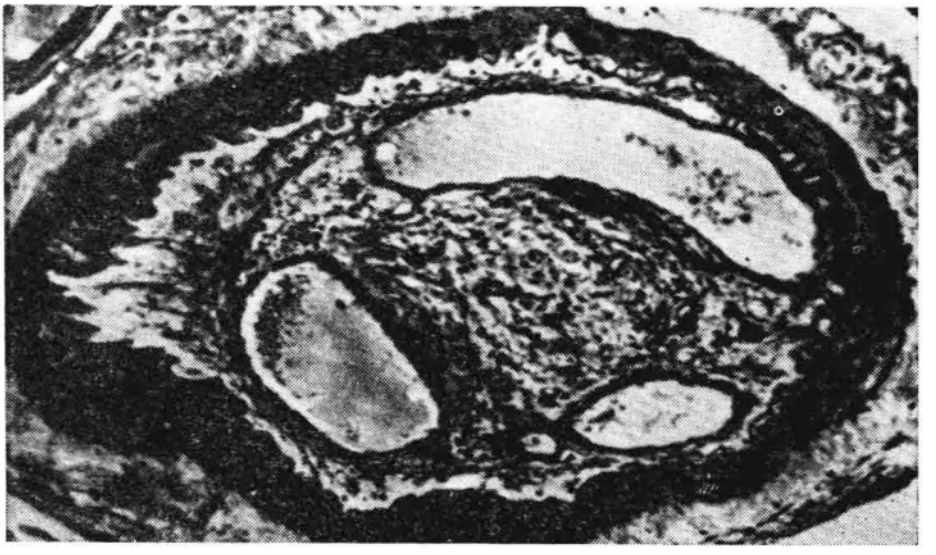

Fig. 6. Thromboangiitis obliterans. Inferior, posterior cerebellar artery. Endothelial proliferation with considerable obliteration of the vascular lumen

glia. Erythrocytes repleting the vessels are fairly visible in some of the vessels while forming a homogeneous mass in the others. (Fig. 6.)

In Nissl's preparations, capillaries which are normally barely perceptible resemble thick rings, endothelial nuclei penetrating their orifices in many places. Patches of softening have their usual appearance: it may merely be noted that they often are distributed in stripes and lines in the direction of the small vessels. A mild inflammatory infiltration, which should be regarded as a reactive one, evident in the membranes over the cortex in the occipital region. Small patches of softening which were formed at different periods in the cerebral cortex. Granular balls containing haemosiderin evident in the preparations taken from the cortex of the occipital region. Extravasates observed around the vessels in the thalamus.

Proliferation of vascular endothelium evident in the thalamus and in the occipital cortex. Proliferation of endothelium spreads to the minutest vessels, arterioles and capillaries. The muscular membrane and the elastica remain intact. Proliferation of endothelium leads in some places to the complete obliteration of the vascular orifices. Cicatrising and atrophical changes evident in the cerebral cortex distributed in accordance with granular atrophy. All the cells destroyed in the upper regions of the occipital cortex: considerable glial growth is observed. The IV stratum is preserved partially, the V and VII strata of the cerebral cortex greatly rarefied.

Most noteworthy in the histopathological examination were two facts: 1) proliferation of the vascular endothelium; 2) extreme hyperaemia of the vessels, extravasates and thrombi in varying stages of development. Vascular dilatation and hyperaemia are regional. While stasis is distinctly visible in regions which receive their blood supply from distal sections of the cortical branches of the posterior cerebral artery, it is less pronounced in the frontal and temporal cortex and completely invisible in the white substance. A picture of red stasis is observed. Here and there are scant perivascular accumulations of white corpuscular elements corresponding to the picture of leukodiapedesis concomitant with stasis. Changes in the nervous system may be summed up as follows: diffuse focal destruction of tissue depends upon disturbance of the blood supply in consequence of contraction or occlusion of the vascular orifice. (Fig. 7.)

Most conspicuous in histological examinations in other cases are proliferative changes in the vascular intima. Granulation tissue, rich in fibroblasts, is evident under the endothelium of the intima. Thickening and hyperplasia of the intima leads to contraction of the vascular orifice, with partial, or, in some cases, with the complete obliteration of the orifice. Proliferative changes spread through the whole width of the intima, thrombi being evident in some cases in the major vessels. The elastica is usually preserved. Only in far advanced cases of proliferation is it possible to find in the elastica a certain degree of atrophy and degeneration. There are practically no changes in the muscular membrane and in the adventitia. Only in the case of a fresh vascular lesion is it possible to find perivascular accumulations of lymphocytes and leukocytes which are evident in the thrombus itself. Changes are observed also

in the pial veins of medium size and in minor arteries. Capillaries are also affected in some cases. In other cases haemorrhages into the vascular walls may be found. The endothelium seems swollen and wedges into the vascular orifice. The nuclei of the muscular membrane also swell up in the same way. Subendothelial cells of the intima are

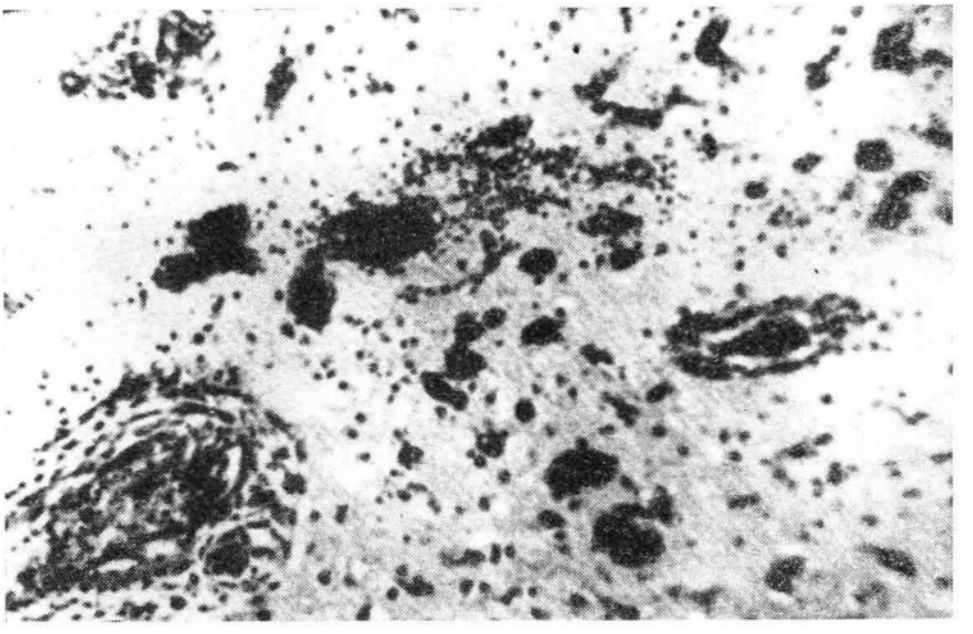

Fig. 7. Thromboangiitis obliterans. Formation of thrombi in the minor cerebral arteries. Stasis and microscopic diapedetic haemorrhages

affected by necrosis. Subsequently the blood in the vascular wall resolves and necrobiotic changes are succeeded by reactive cellular, chiefly fibroplastic, proliferation.

Subsequently scars are formed, chiefly in the shape of fibrosis, proliferation of connective tissue fibers. The following changes are found in the nervous system: diffuse patches of softening which contain a considerable amount of granular balls, small patches of gliotic scars, patches of rarefied cerebral tissue. Extravasates of different sizes are found in some places around the vessels; in some cases

they become numerous and may be distinguished macroscopically in the form of more or less extensive haemorrhages.

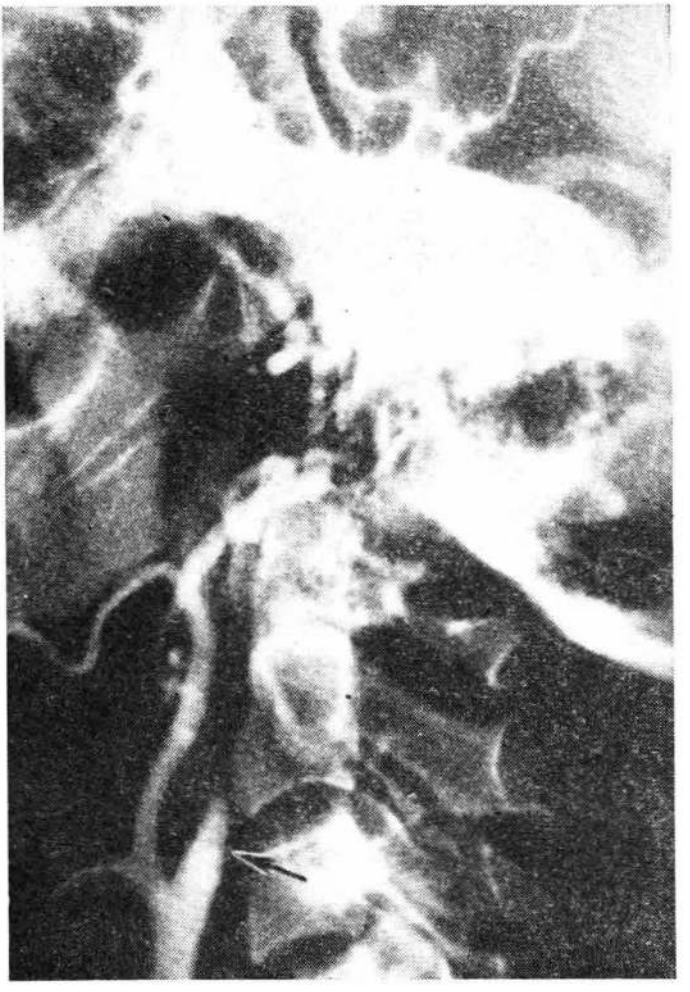

Fig. 8. Thrombosis of the internal carotid artery in thromboangiitis obliterans. Arteriography. Thorotrast blocked in the internal carotid artery at a point 2 cm above its deviation

The development of changes in the cerebral vessels may be divided into two stages: the necrobiotic and the proliferative stage. The intima is thickened and closes up the orifice. The endothelium degenerates and forms secondary thrombi which obstruct the vessel completely. (Fig. 8.)

The morphological picture affords ground for the assumption that the process begins with obstruction of vascular innervation. Proof in support of this viewpoint is afforded also by the paroxysmal nature of the clinical symptoms and the regional type of cerebral stasis. The following observation may serve as an illustration to it. For many years a patient was suffering from migraine attacks with the loss of vision and objectively established vascular spasm in the retina. That was later followed by a stable disorder of vision and paralysis of the extremities. A histological examination revealed changes in the vessels of the brain and retina which are typical of thromboangiitis. However, even if the existence of a spasm is taken for granted, it does not explain the cause of histological changes in the vessels. Vascular spasms are frequent and protracted in Raynaud's disease, but they do not lead to arterial changes characteristic of thromboangiitis obliterans. The fact that the disease affects men more frequently than women suggests the involvement of a hormonal factor in the pathogenesis of the disease. Addiction to tobacco is frequently observed, but this factor is not found in all cases.

The development of thromboangiitis obliterans passes through several stages. The disease begins with functional vasomotor disturbances. Recurrent and protracted disturbances condition structural changes in the vessels which in their turn produce secondary lesions in the nervous system. There can be no doubt today that other vascular diseases pass through the same stages.

D. I. Panchenko finds in the development of thromboangiitis obliterans an analogy with the hypertensive disease, "with its complex process of formation of functional and organic vascular insufficiencies".

N. V. Rozovsky and V. N. Chernigovsky emphasise the leading role played by nervous disturbances in the pathogenesis of thromboangiitis obliterans. In their opinion, a constant flow of impulses emanating from the oxygen-

deficient tissue of the extremities produce reflex changes in the vascular tone. Consequently, stimulation of the ischemic tissue receptors intensifies the vasospasm. The result is a vicious circle, the entire nervous system being involved in the process.

Modern pathologists and clinicians consider thromboangiitis an allergic disorder with a sensibilisation to various allergens and a hyperergic vascular reaction (A. I. Abrikosov, E. Y. Gertsenberg, F. M. Tareyev and N. A. Kurshakov). The disease is "identical with periarteritis nodosa, the difference in their morphology being probably determined by the fact that in the former, owing to lesser sensitiveness of the vessels, or owing to lesser sensibilisation, the process in the vascular walls acquires almost an exclusively proliferative character expressed in the expansion of subendothelial tissue". (M. A. Skvortsov.)

The diagnosis has to be differentiated from the vascular form of cerebral syphilis and atherosclerosis of the brain. A negative Wassermann test of the blood and cerebrospinal fluid and the absence of pleocytosis in the cerebrospinal fluid exclude the possibility of syphilis. Cerebral atherosclerosis affects people of a more advanced age, but the age limits for both diseases are so wide that this symptom does not always carry adequate conviction.

Certain diagnostic value is attached to capillaroscopy which reveals a spasticoatonic syndrome with predominant stasis: repeatedly contracted and stretched loops, structural changes in the walls of the capillaries with the formation of thickenings and swellings. It is, however, impossible to agree with the concept that capillaroscopy is a decisive diagnostic factor since similar changes may be observed also in other disorders, in the hypertensive disease in particular.

It may sometimes be difficult to differentiate between thromboangiitis and a cerebral tumour. Acute development of symptoms, remissions alternating with exacerbations, bilateral symptoms in some patients and the absence of

signs of a rise in intracranial pressure make it possible to exclude the possibility of a cerebral tumour. Encephalographic and ventriculographic examinations reveal the absence of dislocations and deformation of the cerebral ventricles which are characteristic of tumours.

Initial symptoms of thromboangiitis are sometimes mistaken for atypical forms of multiple sclerosis, inasmuch as the disorder may begin with transient symptoms of the cranial nerves and continue with long remissions. What distinguishes this disease from disseminated sclerosis is the presence of headaches, prevalence of cortical symptoms as well as the absence of disseminated spinal and cerebellar symptoms.

A differential diagnosis should be made with due account to the fact that thromboangiitis is a general disorder of the cardiovascular system. From the standpoint of terminology, the "purely cerebral type of thromboangiitis" is quite conditional. Nervous symptoms may predominate in the picture of the disorder, but a thorough examination reveals vascular changes in other organs.

The clinical picture contains no characteristic nervous symptoms. A typical factor is the alternation of exacerbations with remissions, the polymorphic character of the symptoms. Only when changes are found also in other vessels, chiefly, in those of the extremities and eyeground, is it possible to speak definitely of the character of the disorder.

If a patient between the age of 30 and 50 is found to be suffering from slowly progressive cerebral symptoms, with exacerbations and remissions, concomitant with the absence of pulsation in the peripheral vessels, cyanosis of the toes, numbness, trophic changes in distal parts of the extremities, attacks of pain in the region of the heart and intestines, then it is not difficult to make a diagnosis. Consequently, all the patients suspected to be suffering from thromboangiitis should be examined for the absence of pulsation in the lower extremities. As soon as symptoms

of intermittent claudication appear, it is necessary to eliminate at once all influences promoting the development of the disease: smoking, prevention of repeated and protracted frigorism. The regimen of life and work are in the main the same as in atherosclerosis.

Treatment of cerebral symptoms coincides with ordinary treatment of the disorder. Indicated treatment: administration of nicotinic acid, Vitamin B_1, testosterone, and pachycarpine per os. D. I. Panchenko recommends intravenal injections of 5-10 ml of a 0.5% solution of novocaine, as well as injections of a 40% solution of glucose.

Anticoagulants, as our experience has shown, are not effective. Foerster and Guttmann recommended the surgical removal of the cervico-sympathetic ganglia. Improvements were observed by them in four cases.

PERIARTERITIS NODOSA

Nervous lesions are observed very frequently in cases of periarteritis nodosa. In the very first description of this disease, Kussmaul and Maier reported a rapidly progressing paralysis of the extremities. According to M. D. Zlotnikov's summary statistics, the peripheral nervous system is involved in the process in 25-27 per cent of cases, and the central nervous system—in 30 per cent of the cases. On the basis of contemporary clinical observations it may be assumed that symptoms showing that the nervous system is involved in the process may be found in every patient suffering from periarteritis nodosa (R. V. Volevich). Nervous signs, and pain especially, may sometimes be the first symptoms of the disease. Still more often they are the most conspicuous factors in the clinical picture and make the patient consult a neurologist in the first place.

The clinical picture of periarteritis nodosa is exceptionally variable. The peripheral nervous system is most frequently affected. The picture of polyneuritis observed

in this case is distinguished by features which give sufficient ground for suspecting periarteritis nodosa.

Severe pain is observed almost constantly. It may often be of a shooting, burning and causalgic nature. The pain is greatly intensified by pressure upon the muscles of the extremities and nerve trunks. Pain may precede the appearance of motor disturbances, but ordinarily the neuritis is of a mixed nature causing paralysis, disappearance of reflexes and sensorial disturbances. The ischiatic, tibial, median and ulnar nerves are affected most often. Peripheral nerves are drawn into the process one after another. Asymmetry in lesions of the extremities is observed in most cases. In many patients an arm is affected on one side and a leg on the other side. A picture of symmetric polyneuritis may be observed in a far advanced stage of the disease; nevertheless, a thorough study of the stages of development of the disorder reveals that the nerves are affected gradually, one after another, in a series of consecutive mononeuritic attacks. Consequently, an asymmetrical polyneuritis is characteristic of periarteritis nodosa. The clinical picture presents as it were a sum of lesions of separate nerves, each affected to various degrees and at different periods. As a rule, one extremity is affected more than the other, paresis beginning in a proximal region of one extermity and in a distal region of the other extremity.

This clinical syndrome is best characterised by the term "phasic multiple neuritis", rather than "polyneuritis". This specific nature of peripheral lesions in periarteritis nodosa is explained by the involvement of the nerves into the process as a consequence of the disturbance of their nutrition owing to the occlusion of the vascular orifices.

As compared with the pronounced and constant nature of the changes in the spinal nerves, symptoms of nervous lesions recede into the background, although they too are observed quite frequently. Symptoms of focal lesions of

the cerebrum, such as hemiplegia, aphasia, hemianopsia, convulsive seizures and extrapyramidal hyperkinesis, are observed along with general cerebral symptoms expressed in headaches, vomiting and disturbances of consciousness. These cerebral symptoms usually appear suddenly, the process resembling a cerebro-vascular accident. In fewer cases they develop gradually. Subarachnoid haemorrhages are also observed producing a picture of acute meningitis. Psychic disturbances, and especially Korsakoff's syndrome are also observed. Noteworthy also are symptoms of cerebral oedema which may lead to the erroneous diagnosis of a cerebral tumour.

Our following observation may serve as an example.

Patient K., 36 years of age, considers himself ill since 1945, when pain in the left leg appeared and he was running a high temperature for two weeks. A feverish state was again observed in 1946 when the case was diagnosed as malaria. A feeling of numbness and pain in the left leg appeared in March 1947. Headaches appeared in May and an attack of giddiness on August 9. On August 10, the temperature rose to 39° C. On August 11, the patient was brought to the hospital. On admission a state of psychomotor excitement, clouded consciousness, occipital rigidity and faintly expressed Kernig's sign; the patellar and left Achilles tendon reflexes absent. Reduced superficial sensitiveness of the left ankle and sole.

Blood count: Hb 58%, leukocytes 13,700, eosinophils 2%, band cells 4%, neutrophils 80%, lymphocytes 8%, monocytes 6%. Urine unchanged. Wassermann's reaction in blood and cerebrospinal fluid negative. Cerebrospinal fluid: pressure 750 mm, albumin 0.75 ‰, cytosis 4.

The patient was transferred to the Institute of Neurosurgery with the diagnosis of arachnoiditis of the fossa cranial posterior. Ventriculography revealed no changes. Several epileptic seizures were observed at the Institute, and symptoms of polydipsia and polyuria were found. Albumin up to 0.66 ‰ appeared in the urine. In October 1947, the patient was transferred to the neurological department of the Botkin Hospital.

At the time of admission on October 15, the patient complained of headaches and pain in the extremities. Marked loss of weight; considerable impairment of memory. Attacks of psychomotor excitement observed. At times visual hallucinations. Vomiting.

Marked occipital rigidity, Kernig's and Laségue's signs, general hyperaesthesia. Impossible to test muscular strength owing to pain; patellar reflex does not respond. Achilles tendon reflexes reduced. Sensitiveness of nervous trunks and muscles when compressed. Temperature subfebrile, blood pressure 210/120 mm Hg. Leukocytosis 6,700-9,000, slight leftward displacement in blood formula, sedimentation of erythrocytes 22-45 mm per hour. Urine: albumin 0.3 $^{0}/_{00}$ and isolated erythrocytes.

Later, the patient developed more pronounced symptoms of cachexia, with elective muscle atrophy of the lower extremities, more expressive on the left side. State of restlessness alternating at times with prolonged spells of sleep. Achilles tendon reflexes disappeared. Decubitus appeared in the region of the sacrum and the buttocks.

The patient died on February 19, 1948. Clinical diagnosis: periarteritis nodosa.

Pathological diagnosis: Periarteritis nodosa with predominant lesion of the vessels of the heart, kidneys and brain; hypertrophy of the left ventricle of the heart; nodal nephrocirrhosis; multiple patches of softening and haemorrhages in the cerebral substance, extreme emaciation, decubitus.

In the case described above, symptoms of multiple neuritis which began with pain in the left leg, were concomitant with epileptic seizures, symptoms of high intracranial pressure, as well as symptoms indicative of diffuse foci in the cerebral hemispheres and in the hypothalamus. Cerebral symptoms were expressed at the beginning in acute attacks alternating with more or less prolonged remissions.

Inasmuch as lesions of the kidneys and hypertension were observed at the onset of the disease, it is clinically difficult to distinguish between cerebrovascular symptoms conditioned by periarteritis and those produced by arterial hypertension. It should be borne in mind that arterial hypertension in periarteritis nodosa may be not only a symptom but also a pathogenetic factor responsible for a number of cerebral symptoms.

Changes in the eyeground such as dilatation of veins, papilloedema taken into consideration and blood effusions into the retina should be noted. Along with the picture

of hypertensive retinitis, exfoliation of the retina, thrombosis of the central artery of the retina and nodules along the arteries have also been described.

The cerebrospinal fluid frequently contains a high amount of albumin; high tension of the fluid and pleocytosis are observed in some cases, a haemorrhagic or xanthochromic fluid—in rare cases.

Characteristic of the pathological picture of periarteritis nodosa is the nodulation of the blood vessels, chiefly of the small arteries and arterioles. A histopathological examination reveals arteritis with hyalinosis and fibrinoid necrosis of the arterial wall. First of all, hyalinosis affects the internal part of the muscular coat and the region under the intima with a resulting local destruction of the muscular and elastic tissues. This is followed by the thickening of the entire wall and the development of panarteritis. Cellular reaction with considerable proliferation of leukocytes, lymphocytes and eosinophils, and, in some cases, the appearance of giant cells, begins in the vascular walls, and, especially in the tunica adventitia. Destruction of the vascular walls leads in some cases to the formation of aneurysms sometimes with a subsequent rupture and a haemorrhage.

Exacerbations and remissions of the process are reflected in the histopathological picture. The acute stage is characterised by a rapid development of necrosis of the muscular coat of the arteries, while the elastic fibers disintegrate into segments and often disappear altogether. During the remission some vessels show a tendency towards improvement expressed in the appearance of new elastic tissue and in the replacement of the necrotic muscular tissue by a connective tissue cicatrix. The lumen of the vessel may also be rehabilitated.

In the periadventitial space only a small number of lymphocytes may be observed in this case. The process is of a systemic nature and it affects the vessels of the

nervous system, heart, kidneys, pancreas, muscular system and the intestines.

Necrobiotic, proliferative and sclerotic changes, which are characteristic of periarteritis nodosa, are found in the vessels of the peripheral nerves. Arteritis in different stages, reflecting exacerbations and remissions, may be found in the same patient. (Fig. 9.)

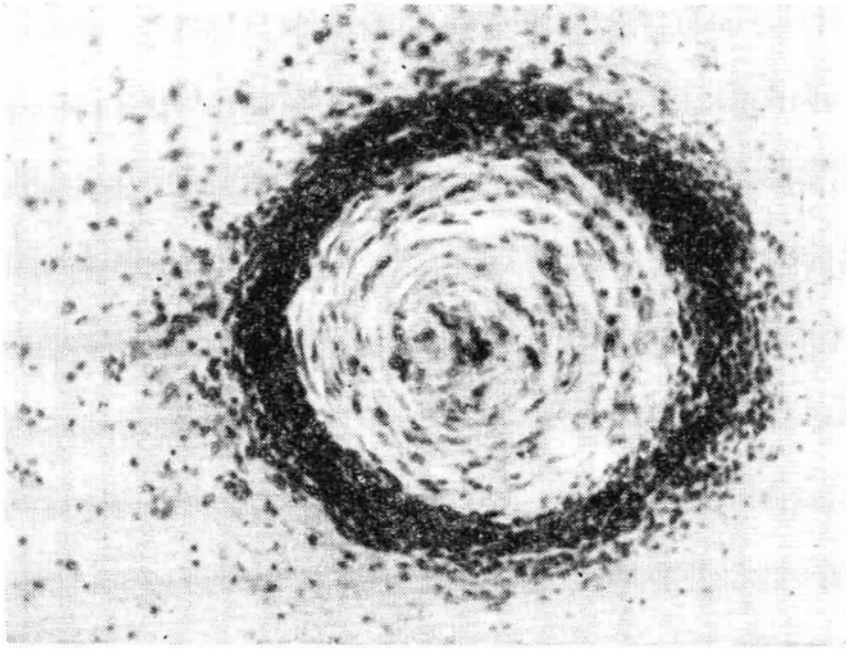

Fig. 9. Periarteritis nodosa. A cerebral vessel. Proliferation of connective tissue, considerable vascular and perivascular infiltration

Inflammatory changes in the form of perivascular infiltrations composed of lymphocytes, and to a lesser degree of eosinophils, and also of isolated plasma cells, are observed in the perineural and endoneural regions. Changes in the vascular walls of the peripheral nerves are quite polymorphous. Proliferation of the intima observed in some arteries is so intensive that it may lead to the obliteration of the lumen. Hyalinosis develops in the muscular

coat. In the obliterated vessels the lumen is closed by granulation tissue which in some cases is abundant with newly-formed vessels containing blood. A more or less pronounced infiltration around the vessels is observed along with necrosis and sclerotic changes of the vessels. Massive infiltrations, hyalinosis of the muscular coat, endothelial

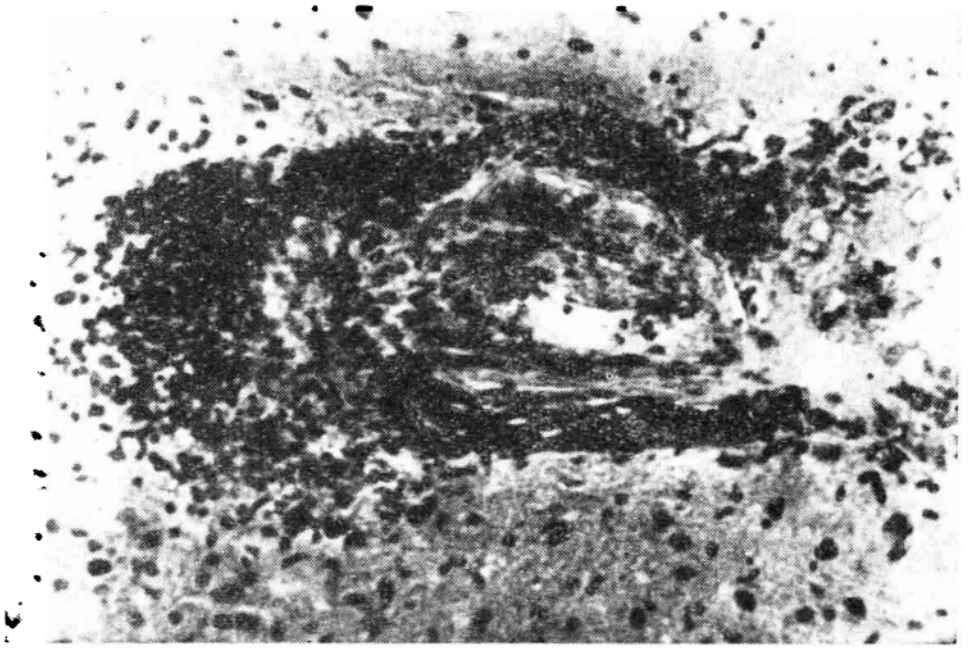

Fig. 10. Periarteritis nodosa. Massive infiltration in external parts of necrotically changed walls of a cerebral vessel

proliferation and sclerosis with vascular obliteration may be observed in the vessels of a peripheral nerve in the same case. (Fig. 10.)

By staining the myelin of the peripheral nerves it is possible to reveal its degeneration in the form of bundles or, which is rarer, in segmental demyelination. In some cases demyelination is less pronounced, extending only to some of the fibers of some peripheral nerves. In these cases, fragmentation, or demyelination, is observed in some of the bundles, while the other fibers remain intact. When

the axial cylinders are stained, disintegration and fragmentation of these cylinders can also be found in some of the preparations.

Demyelinaton of peripheral nerves is a consequence of lesions of the nutrient nerve vessels, of partial or complete obliteration of their lumen. Owing to the specific nature

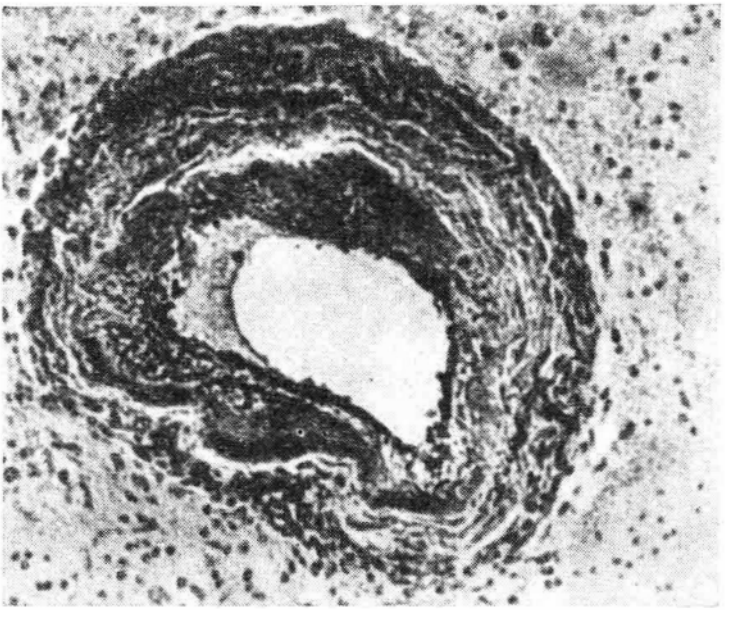

Fig. 11. Periarteritis nodosa. Fibrinoid necrosis of an arterial wall in the cerebrum

of the blood supply of the peripheral nerves, the degenerated nerve fibers are found dispersed in different nerve bundles, rather than in compact shape, if a lumen is obliterated. The blocked section of the vessel may be revealed proximally to the degenerated nerve. On the other hand, at the level of the vascular lesion the nerve may be normal, or changed very little. (Fig. 11.)

Macroscopic changes in the central nervous system are rarely observed. Foci of blood effusions and patches of softening may sometimes be observed in the cerebrum and spinal cord. A microscopic study reveals vascular changes

in the central nervous system characterictic of periarteritis nodosa. The middle coat of the affected vessels is stained bright red by eosin; the homogenised mass is almost completely devoid of cellular elements (fibrinoid necrosis). The cells of the intima remain, and cellular proliferation is observed in the tunica adventitia. In other vessels the muscular coat is of uneven thickness, defibrinated and in places has a homogeneous fine-granuliform appearance and is characterised by a scarcity of cells. The orifices in some of the vessels are contracted owing to endothelial proliferation. Fresh or old thrombi are observed in some of the vessels with changed walls. In some of the vessels the walls are greatly thickened owing to the growth of connective tissue; the tunica adventitia contains a great deal of lymphoid cells and fibroblasts, with considerable cellular infiltrations. In cases where clinical symptoms indicative of cerebral lesions were absent, our histopathological examinations revealed neither changes in the vascular walls nor infiltrations. However, perivascular oedema of various intensity and histiocytic proliferation are evident in all cases. (Fig. 12.)

In general, necrobiotic and proliferative, as well as sclerotic changes, characteristic of periarteritis nodosa, are found in the cerebral vessels and in the vessels of the peripheral nerves. Different stages of arteritis reflecting exacerbations and remissions are found in the same patient.

In fewer cases, greater or smaller nodes of demyelination may be observed in the cerebrum and spinal cord. In some places the small nodules merge into a large node with an irregular border. This picture of demyelination has given Balo the ground for considering these changes analogous to those described in periaxial encephalitis. In seven out of 14 cases Balo found the pancreas affected by periarteritis nodosa. Concomitant changes in the peripheral nerves were found in six of these cases, and demyelinating encephalitis—in one case. Balo does not consider it an accidental coincidence; he puts forward a hypothe-

sis, assuming that changes in the nervous system are caused by lesions of the pancreas which secrete substances destructive to the brain lipoids. It is known that fatty necrosis of the pancreas often leads to grave intoxication of the organism. Balo's viewpoint is not convincing inasmuch as in many cases characteristic changes have been found in the nerves in the absence of lesions of the pancreas.

Focal changes in the cerebrum may also be caused by thrombosis of the small cerebral vessels, or by haemorrhages. The involvement of meningeal vessels in the cerebral vessels any subarachnoid haemorrhages.

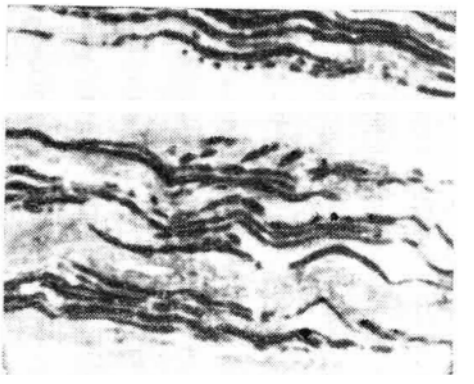

Fig. 12. Periarteritis nodosa. Fibular nerve. Myelin fragmentation and disintegration

It may happen, however, that the most thorough examinations fail to find in the process may lead to changes which could cause demyelination. It should then be assumed that the latter is conditioned by the same cause as the vascular changes.

Considering the fact that today all the pathologists define periarteritis nodosa as an allergic disease which has as its basis the sensibilisation of the organism by various allergens, it may be assumed that demyelination is a consequence of the allergic reaction of the cerebral tissue.

The question of the role of allergic reactions in the pathogenesis of demyelinating diseases of the nervous system has been the subject of widespread discussions of late. Antirabic vaccinations in encephalitis enabled us to understand better the nature of immunity in the nervous tissue. The difference in the pathological anatomy of rabies and encephalitis after antirabic vaccinations suggests the idea that a post-vaccinative encephalitis is not induced by the rabic virus, but that it is a result of sensibilisation of a human nervous

system by the nervous tissue of a rabbit. It has been proved experimentally that the suspension of a normal homologous brain is not an antigen, but that a cerebral autolysate, or nervous tissue infected by the vaccine acts as an antigen for animals of the same species. The degree of demyelination is proportionate to this antigenous action of the cerebral autolysate (Beiley and Gardner). Ferraro, who injected an antigen into the brain of monkeys, described two types of lesions: 1) necrotic, at the place of injection of the antigen, and 2) distal nodes of perivascular demyelination.

In the light of these investigations, the origin of demyelination may be presented as follows. Even initial vascular lesions affect the metabolism of the myelin membranes and cause their partial disintegration. Penetrating into the blood, the product of disintegration of myelin induces the formation of specific antibodies. When the latter attain a certain degree of concentration they pass into the central nervous system and form foci of demyelination in the white substance. Consequently, an allergic process may be one of the causes of demyelination in the central nervous system.

The concept that periarteritis nodosa is an independent disease with an unknown pathogenic agent has very few supporters. Almost all the pathologists agree that periarteritis nodosa is an "allergic disease which has at its basis the sensibilisation of the organism by means of various allergens with subsequent hyperergic reactions of the vessels in different parts of the organism" (M. A. Skvortsov). The difference between periarteritis nodosa and other forms of vascular reaction is explained by many pathologists by the hyperergic nature of the inflammatory reaction in consequence of the preceding toxiinfectious factors.

Attempts have been made to explain the increase in the incidence of periarteritis nodosa in recent decades by the toxic action of sulfanilamides used in the treatment of this disease. In some cases, an infection or intoxication found in the case history of patients may be considered the cause of the disease. Apparently, primary disturbances in the immunity mechanisms of these patients provoked a number of consecutive chain reactions.

Despite the proximity of periarteritis nodosa to thromboangiitis obliterans, it is possible in most cases to dif-

ferentiate these diseases. Unlike periarteritis nodosa, thromboangiitis obliterans is very rarely accompanied by pronounced multiple neuritis. Neuritis found by D. I. Panchenko in histological examinations produce practically no clinical symptoms. Only in one patient did we observe the disappearance of the patellar reflex without any other symptoms of polyneuritis. Even in very advanced stages of thromboangiitis obliterans we have not observed any distinct symptoms of neuritis of the ischiatic or femoral nerves.

The morphological picture of these diseases also differs essentially: thromboangiitis is marked by massive endothelial proliferation with subsequent contraction of the lumen, proliferative phenomena being very rarely complicated by inflammatory or necrotic changes; periarteritis nodosa—by minimal secondary proliferation of the intima, the latter being changed in the terminal stage only.

Thus, although these diseases have many features in common, there are considerable distinctions between them which make it possible to differentiate them clinically. These distinctions are of practical value as well, inasmuch as periarteritis nodosa is a more malignant process.

Lately, an attempt has been made to classify a number of diseases which resemble periarteritis nodosa in one group of collagen diseases (collagenosis). It includes, in addition to periarteritis nodosa, rheumatism, rheumatoid arthritis, lupus erythematosus, sclerodermia and dermatomyositis. The term "collagenosis", or "collagen disease", was first proposed by Klemperer in 1942. Collagenous elements of the connective tissue consist of collagenous fibers and the basic substance which constitute the connecting frame of the synovial and serous membranes, the endocardium and vascular walls. Pathomorphological changes in collagen diseases include distinctive fibrinoid degeneration, frequently expressed in necrosis, cellular proliferation, infiltration and sclerosis in cases when the lesion is not very intensive.

Multiple vasculitis may also be a feature of the pathomorphological picture.

The theory of the collagen diseases has made a new contribution and has broadened our ideas about connective tissue, but from the clinical standpoint it has merely indicated the existence of transitional forms between dermatomyositis and sclerodermia, lupus erythematosus and periarteritis nodosa, etc. The real relationships between these diseases will become clear only when the etiology of periarteritis nodosa in one case and rheumatoid arthritis in another case is known, in other words, when the etiology of each collagen disease is determined.

At present, the theory of collagen diseases may be regarded as an attempt to group together, on the basis of morphological data, a large number of diseases with different clinical pictures, with no indications pointing to the unity of their etiological and pathogenic nature. Similarity of the histological picture may be explained by a limited number of tissue reactions to numerous injuries. Distinctions and similarities are determined not only by the virulence, concentration, duration of the action and point of application of the harmful agent, but also by the resistance of the organism and the reactivity of its separate organs. Consequently, histopathological data should be correlated with the clinical picture of the disease. The existence of common features in the diseases related to the collagen group, with the differences in their clinical pictures, the course of disease and its outcome, prompts the clinicist to study the questions connected with a differential diagnosis.

Selye defines periarteritis nodosa as an adaptation disease in which no definite specific biochemical or infectional cause is found, and where the stress of the organism is the decisive factor. The disease develops through a system of hormones and represents the final phase in stages of "resistance and exhaustion". By inoculating rats with large doses of desoxycorticosterone and keeping them on

a salt-rich diet, Selye observed symptoms of nephrosclerosis, arterial hypertension and a histopathological picture of periarteritis nodosa. The same picture was obtained after the administration of desoxycorticosterone and the pituitary somatotropic hormone. Selye believes some of the collagen diseases, and periarteritis nodosa in particular, to be adaptation diseases. Under the influence of non-specific "aggression", irritation of the pituitary gland stimulates the adrenal glands which react by an intensification of the secretion of mineral corticoids which are not compensated by glucocorticoids. This disturbance of equilibrium determines the action of the mineral corticoids on the endocrinic function of the kidneys and calls forth a glomerular affection, hypertension and lesions of the arteries of the type of periarteritis nodosa. After the administration of cortisone, glucocorticoid causes a rapid disappearance of these symptoms.

The kidneys play a very important part in the origin of arterial lesions. By performing a partial ligation of the arteries in rats so as to equalise arterial pressure with intrarenal pressure, Selye produced a rapid and distinct change in the kidney, which he called "endocrine kidney". The author induced periarteritis nodosa in the rats which underwent this operation. The arteritis thus produced was cured by cortisone.

A diagnosis may be made by comparing the symptoms indicative of lesions of the nervous system and those of the visceral organs. The claim often made that periarteritis nodosa is diagnosed in life in exceptionally rare cases, mainly in the presence of cutaneous lesions and biopsy, should be considered obsolete. As far back as 1946, M. A. Skvortsov wrote in the manual *Pathological Anatomy of the Main Diseases of Childhood* that "clinical manifestations of this disease are so varied that it makes a diagnosis during the patient's life practically impossible". At present the disease is usually diagnosed during life. We have made a correct diagnosis in 11 out

of 14 cases of periarteritis nodosa under our observation.

The clinical picture of the disease is distinguished by a great variety; however, despite the absence of symptoms which are pathognomic for this disorder, the combination of nervous symptoms with long periods of high temperature, leukocytosis in the blood and high erythrocyte sedimentation, cachexia, various symptoms of lesions of the kidneys, heart and the gastrointestinal tract, furnish the basis for an accurate diagnosis.

The combination of asymmetrical polyneuritis with high temperature and cachexia should always warrant the assumption of periarteritis nodosa.

Owing to frequent remissions, the *course* of the disease may cover a period of several years. Nevertheless, until very recently the prognosis was unfavourable. Treatment with sulfanilamides and antibiotics produced no effect.

With the introduction of the adrenocorticotropic hormone and cortisone into medical practice, there have been reports of the successful treatment of periarteritis nodosa with these preparations. Shick, Baggenstoss and Polley described the results produced by treatment with cortisone and the adrenocorticotropic hormone. An improvement in the condition of all the patients was observed within 24-72 hours. The temperature became normal and erythrocyte sedimentation returned gradually to norma. A certain turn for the worse was observed again after the treatment had been ceased. Three of the patients had been in an extremely grave condition before the treatment; two of these patients died of disturbances in renal and cardiac functions. A severe progressive hypertension persisted in other cases and symptoms of hypercorticoidism appeared.

Favourable effects in the first 24-72 hours of treatment were also observed by Z. M. Getmanskaya, R. A. Semyonova and G. N. Sokolova. The adrenocorticotropic hormone is apparently not as effective as cortisone.

We present our own observation.

Patient S., age 39, was brought to the neurological department of the hospital on August 3, 1954 with the diagnosis of meningoencephalitis. The patient did not recall any previous diseases.

Rapid fatigability in the legs appeared in 1952, and since then the patient was troubled by pain in the left leg towards evening. Painful sensations were followed by oedema which grew at the end of the day, but the patient kept on working. In July 1954, a feeling of general indisposition and pain in the right leg appeared. On July 21, he had to stay in bed: the pain in the legs became more intense and the temperature went up to 39.6 °C. At the end of July the pain extended to the upper extremities, first to the right arm and then to the left one; pain in the back, nausea and vomiting appeared, concomitant with periodic diplopia.

At the time of admission the patient was in full consciousness but extremely exhausted. Evident diffuse cardiac apex beat, the heart boundaries dilatated to the left. Arterial pressure 130/80 mm Hg. Edge of the spleen palpable.

Strabismus divergence and diplopia. Tetraparesis, more pronounced in the distal parts of the extremities. Tendon reflexes in the arms and patellar reflexes—brisk. Achilles tendon reflexes could not be elicited. A sensorial lowering in the fingers and feet. Painfulness produced by palpation of nerve trunks. Atrophy of interosseal muscles of the wrists and feet.

During the patient's stay in the hospital paresis of the extremities began to progress rapidly, arterial pressure rose to 190/100 mm Hg, leukocytosis of the blood—to 16,000, erythrocyte sedimentation—to 52 mm per hour and temperature—to 39° C.

The progressive course of the disease and combination of visceral lesions with progressive asymmetrical polyneuritis, leukocytosis of the blood and high temperature suggested the diagnosis of periarteritis nodosa.

Treatment with adrenocorticotropic hormone, in doses of 20 units daily, was given from August 7 to August 21, 1954. Despite the treatment, paresis in the extremities developed into paralysis, atrophy of interosseal muscles of the wrists and feet and cachexia progressed. Epileptic seizures began on August 28. On October 9, after a series of such seizures, the patient's condition took a severe turn for the worse and he lapsed into an unconscious state.

Treatment with cortisone began on November 11. Forty-eight hours after the beginning of this treatment a sharp improvement was observed in the patient's condition; he regained consciousness, the temperature fell and the attacks abated. Eventually the patient's condition continued to improve and arterial pressure to fall. Leukocytosis and erythrocyte sedimentation dropped to normal. Pain in

the extremities disappeared, their volume of movements grew considerably, and the patient gained a great deal of weight.

Altogether, the patient received 7.9 g of cortisone. At the end of the treatment hypercorticoid symptoms appeared: fatty deposits began to take place in the cheeks and abdomen, and hyperaemia of the cheeks was observed. Treatment with cortisone was interrupted on November 16, and in January 1955, the patient was discharged from hospital in a satisfactory condition with residual symptoms of polyneuritis.

Beginning with April 1955, pain in the arms and legs started growing in intensity, arterial pressure went up again to 210/100 mm Hg, and on June 8 the patient was returned to our department in the hospital. At the time of admission his arterial pressure was 240/140 mm Hg and a systolic murmur was distinctly heard at the apex. Periodic subfebrile temperature, no changes observed in the blood. Signs of nervous lesions, the same as at the time when the patient was discharged from hospital. The condition was gradually deteriorating and the patient died on August 2, 1955.

Pathological diagnosis: Periarteritis nodosa. Nodules along the branches of the coronary arteries of the heart, the mesenteric and renal arteries. Haemorrhage into the wall of the gastrointestinal tract, ulcers in the small intestines. A brown cyst in the sinistral region of the subcortical ganglia and small patches of softening in the cerebrum. Small fatty necrosis in the caudal part of the pancreas. Hypertrophy of the muscles of the left ventricle of the heart. Arteriosclerotic nephrosclerosis, atrophy of the muscles of the wrists and feet.

Histological examinations of the cerebral vessels and viscera revealed an almost complete disappearance of inflammatory symptoms in the vascular walls with fibrous obliteration of their lumen. Only in some of the vessels did the walls present an undistinct picture of cellular infiltration. In many vessels the changes in the walls were similar to those observed in hypertensive disease.

In the given case treatment with cortisone produced a rapid and considerable improvement, but the patient died six months since the termination of the treatment. A histological examination showed that the process developed into fibrosis. Death was caused by secondary hypertension. Consequently, it means that the improvement in the patient's condition was caused by the disappearance of the inflammatory symptoms, and not by the complete rehabilitation of the vascular structure. Fibrosis of the arterial

wall with frequent obliteration of the lumen remains. The picture resembles that observed in spontaneous remission, but the latter is exceptionally rare.

TEMPORAL ARTERITIS

The first report of temporal arteritis was made 60 years ago by Hutchinson. In 1932, Horton, Magath and Brown published a detailed description of the clinical and histopathological picture of this disease. As the name itself suggests, the most permanent and notable symptom of the disease is inflammation of the temporal arteries. Other cranial arteries (occipital, facial and ophthalmic) are often involved in the process. Thus far, about 150 cases of temporal arteritis have been described in world literature. The disease is usually observed in persons over the age of 55-60, with an equal frequency among men and women. It begins with general symptoms such as high fatigability, a feeling of exhaustion, loss of weight, insomnia, anorexia and arthralgia. Before long the temperature becomes subfebrile and pain appears in the region of the temple and occiput. Pain may extend also to the face, eyes, jaws and mandibular joint. Tenderness of the scalp may be so great that severe pain is called forth by touching the pillow or by chewing. The temporal artery becomes painful to palpation and swollen, its pulse is very faint or absent. The skin over the artery becomes red and oedematous. Lymph nodes of the neck and occipital region are enlarged in some cases and become painful. In addition to temporal arteries, occipital and ophthalmic arteries are sometimes involved in the process. Lesions of the ophthalmic arteries are observed in 30-40 per cent of cases. Thrombosis of the central artery of the retina and ischemic neuritis may be found in the eyeground.

Lesion of the ophthalmic arteries often leads to total or partial blindness of one or both eyes.

Organic nervous symptoms are rarely observed. There

are data, concerning oculomotor disturbances, transitory diplopia (Horton and Magath) and transient ptosis (Morin and Cooke). Ataxia, attacks of giddiness and pyramidal signs are sometimes observed. It may be difficult to distinguish these symptoms as well as psychic changes referred to by some authors from symptoms of atherosclerosis in elderly people who suffer from temporal arteritis.

Here are two of our own observations.

Patient B., age 71, was brought to the neurological department of the city hospital on April 20, 1956 with complaints of constant and severe headaches in the dextral temporal and parietal regions, general weakness, rapid fatigability and insomnia.

General weakness, insomnia, pain in the occipital region and anorexia appeared in January 1956. Within a month the pain extended to the region of the right temple and parietal region. It was a constant, acute, shooting pain; by pressing upon the head the pain was sharply intensified. In the dextral temporal region the patient noted a severe swelling of the vessels and pain on touching them. Pain appeared at the same time in the left brachial joint. The temperature became subfebrile (37.5-37.8° C.). A feeling of exhaustion and severe headaches confined him to bed. Treatment with antineuralgic drugs and penicillin produced no effect.

The patient had a well proportioned physique and was of fair nutrition. Heart tones dull. Pulse rate—80 beats per minute. Arterial pressure 120/80 mm Hg. X-ray examinations of the chest revealed a slight dilatation of the heart to the left. Movement of the sinistral brachial joint restricted by pain. Temperature 37.2-37.4° C.

A tortuous, swollen and infiltrated artery with palpable nodules along it evident in the dextral temporal region. Pulsation of the artery slackened, painful on palpation, the skin over it unchanged. Lymph nodes of the neck not enlarged. Pulsation of the extremity vessels distinct. Vision normal. Contraction of the retinal arteries observed in the eyeground. Pupils normal. Organic symptoms of nervous lesions not observed. (Fig. 13.)

Blood count: Leukocytes 10,000, erythrocyte sedimentation 43 mm per hour, cholesterine 100 mg%. Urine normal. X-ray examination of the skull and brachial joints reveals no changes. Electrocardiogram: Sinistral type, horizontal position of cardiac axis.

Treatment with the adrenocorticotropic hormone started on April 25: 10 units at intervals of six hours for the first two days, and during subsequent days—20 units. On May 6, after the injec-

tion of 540 units of the hormone the patient noted a relaxation of the headaches, the temperature dropped to normal, erythrocyte sedimentation dropped to 27 mm per hour. On May 10, severe pain appeared in the epigastric region, repeated vomiting, flatulent abdomen, painful sensations in the region of the left groin, marked peristaltic action in the dextral iliac region. After the injection of pantopon and atropine, and a syphon enema, the pain in the abdomen was relieved, and the patient moved his bowels. Since then the temperature again went up to 37.2-37.6° C.

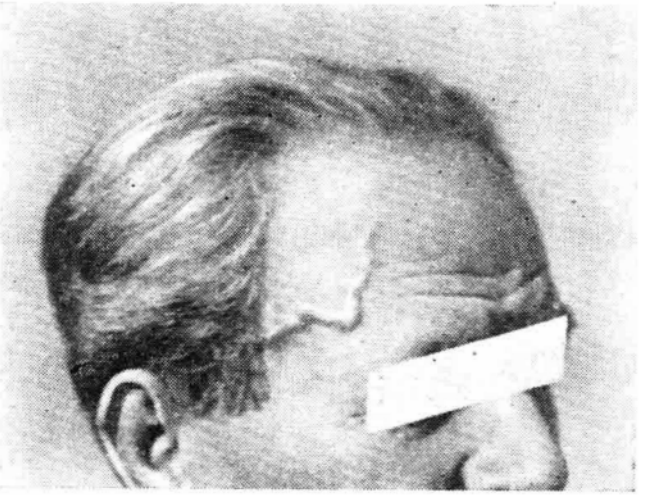

Fig. 13. Temporal arteritis. Drastically thickened, tortuous temporal artery

An incision in the dextral temporal region was made on May 19 under local anaesthesia (novocain). The temporal artery and vein were isolated and partially excised (3 cm of the vein and 2 cm of the artery). After the operation the patient was no longer troubled by persistent dull pain in the temporal and parietal regions. Fatigability abated considerably, sleep became normal, but the temperature remained subfebrile; erythrocyte sedimentation rose to 55 mm per hour. The patient received 1,080 units of the adrenocorticotropic hormone. In June, headaches disappeared, and the temperature became normal. In July, erythrocyte sedimentation dropped to 25 mm per hour. The patient's condition remains good to this day and he makes no complaints.

A histological examination of the bioptic preparation revealed that the arterial walls were permeated by infiltrations composed of lymphocytes, leukocytes and histiocytes. The structure of the

muscular membrane was vague, and nodes of granulation tissue with patches of fibrinoid necrosis were evident in it. Diffuse fibroblasts, histiocytes and epitheloid cells could be seen in the granulation tissue which extends to the tunica adventitia. The elastica was split in a number of places and disintegrated into fragments. Numerous giant cells were visible in proximity to these fragments. In some

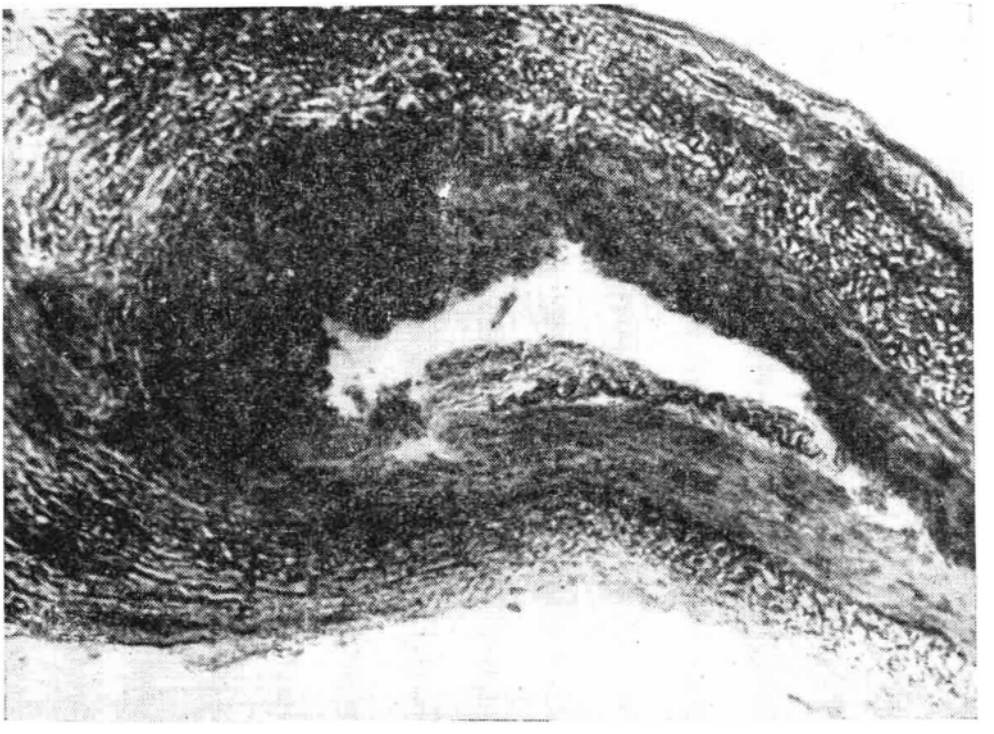

Fig. 14. Temporal arteritis. Wall of temporal artery with leukocyte, lymphocite and histiocyte infiltration. The pattern of the muscular sheath is not distinct and patches of granulation tissue and fibrinoid necrosis are evident in it

places the endothelium was also infiltrated by inflammatory cells. Its integrity was broken, and a thrombus adjoining the intima was taking shape there. The granulation tissue extended also to the adjoining vein the walls of which were thickly infiltrated with inflammatory cells. (Fig. 14.)

Patient M., 57 years of age, was admitted to the neurological department of the City Clinical Hospital No. 4 on November 19, 1955 with the diagnosis of acute meningo-encephalitis. At the time of admission the patient complained of severe pain in the region of the left temple which was radiating into the eyeball. Considers him-

self ill since October 18, when his temperature rose and headaches appeared. On October 21, the temperature dropped to normal, the headaches remained, but their character changed: they were much more severe and localised in the left temple. On October 25, the patient noticed that his left eyelid drooped.

The temporal arteries became heavily swollen and tortuous, especially on the left side. Palpation produced a very painful reaction in the sinistral temporal artery. Its pulse could not be determined. Ptosis of the left lid. No other abnormal nervous symptoms found.

Temperature 37.2-37.4° C. Arterial pressure 180/80 mm Hg. Eyeground normal. Blood count: leukocytes 9,800, eosinophils 2%, band cells 4%, segmented cells 56%, lymphocytes 30%, monocytes 8%; erythrocyte sedimentation 27 mm per hour. Wassermann's reaction in blood and cerebrospinal fluid negative. Cerebrospinal fluid: pressure 180 mm, albumin 0.3‰, cytosis 5.

The patient received 4,800,000 units of penicillin, whereupon the pain in the region of the temple, the swelling and tortuousness of the sinistral temporal artery abated. At the end of December the pain in the region of the temple grew in intensity. Chewing caused a painful sensation in the sinistral mandibular joint.

The temporal artery once again became swollen, tortuous and sensitive to palpation. The temperature rose to 37.9-38.6° C. A fluctuating part was found in the region of the temple. On January 10, 1956, a 3 cm long incision was made in the temporal region. A necrotic mass was discharged; its culture proved to be sterile. Subsequently the patient was no longer troubled by pain. The swelling and tortuousness of the artery gradually disappeared. The temperature became normal.

The clinical picture of these patients, who along with general symptoms of an infectious disorder had local symptoms of inflammation of the temporal arteries, leaves no doubt as to the diagnosis. The probability is not excluded that the acute symptoms of ileus were caused in the first case also by changes in the mesenteric vessels. The fact that a patch of necrosis was found in the temporal region of the second patient does not contradict the diagnosis of temporal arteritis. D. Kendall described a patient who during the disease developed a patch of necrosis in the hairy part of the right temple and in the nasal septum. Formation of necrosis is explained by the clottage of the branches of the temporal artery. The diagnosis in the first case was

confirmed by the histopathological examination of the excised vessel. (Fig. 15.)

The histological picture, just as in our own observation, was distinguished by endo- and mesoarteritis with the formation of granulation tissue and of patches of necrosis in

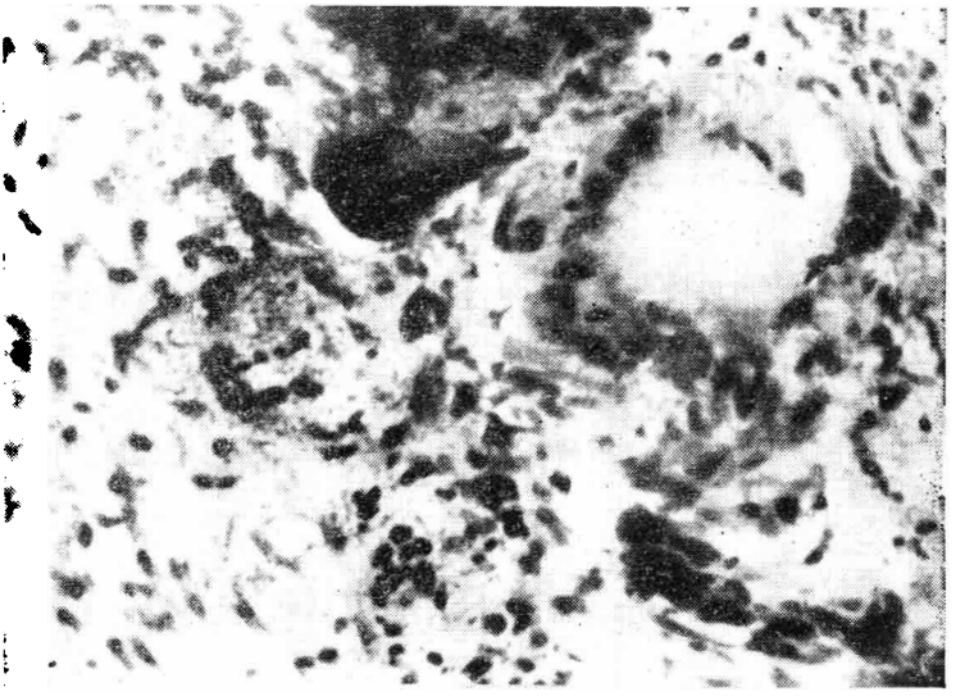

Fig. 15. Temporal arteritis. Giant cells adjoining fragments of disintegrated elastica

the muscular sheath, disintegration of the elastica and the presence of giant cells. In most of the cases described no mention is made of phlebitis. Kilbourn and Wolff both consider the absence of phlebitis a symptom for a differential diagnosis. Nevertheless, the extension of the granulomatous inflammation to the veins is quite possible, and it has been observed not only in our patient (Crosby).

Cooke and his collaborators tried, on the basis of their observations, to trace the dynamics of the process in the

vessels. They found that the inflammatory reaction begins in the tunica adventitia and later extends to the muscular sheath. Still earlier small patches of necrosis appear in it and in the internal elastica. The process may cease at this phase, to be succeeded by recovery. In most cases, however, the morbid process extends to the muscular sheath. The appearance of giant cells, which is characteristic of this disorder, has given Gilmour the ground for calling it giant cell arteritis. (Fig. 15.)

The course of the disease is slow and chronic, with spontaneous remissions. In most of the cases described the disease lasted 8-12 months. All the morbid symptoms usually disappear, but vision is not restored in the case of both total and partial blindness. Relapses are also possible, as it happened in the case of our second patient. The idea of the non-malignant character of the disease has not been fully justified; cases with lethal outcomes have also been described.

Knowing the symptoms of this disease, and with symptoms of temporal arteritis in evidence, it is not difficult to make a diagnosis; but that applies only to a typical course of the disease.

A few years ago we observed two patients of 65 and 70 years of age, who along with signs of a general indisposition and subfebrile temperature had severe headaches and a painful reaction to palpation in the hairy part of the head. It is quite probable that these patients were suffering from temporal arteritis. In a bioptic examination of the temporal artery Morin found changes characteristic of temporal arteritis in two of his patients. Lesions of the ophthalmic arteries, with disturbances of vision and without distinct signs of the involvement of the temporal arteries, are also possible.

Local symptoms supplied the ground for calling the disorder temporal arteritis. This name reflects the most characteristic symptom of the disease, but it does not cover the entire picture of the disease in which local symptoms

are preceded by general symptoms. When Horton and his collaborators named the disorder temporal arteritis, they wanted not only to express the main clinical symptom; they also believed that the disease was localised in these vessels only. The disease was considered not dangerous with spontaneous recovery. Later it was learned that the disease may be fatal.

In 1951, Cardell and Harley described 137 cases of temporal arteritis. Lesions of the eyes were observed in 52 cases; 27 of these patients died. Only in three out of these 27 cases a correct diagnosis had been made before death; in nine cases the course of the disease was atypical and only a histological examination revealed a giant cell arteritis. In 12 out of 27 cases death was caused by cerebrovascular accidents, but a thorough examination of the cerebral vessels was not made. Changes characteristic of temporal arteritis were found in the aorta in 11 cases, in the internal carotid artery in six cases, in the general carotid artery and in the subclavial artery in five cases, in the femoral—in three, in the radial in one case and in the pulmonary artery in one case. These examinations show that the disease affects not only the cranial arteries, and that it may involve into the process other vessels of the organism as well. At any rate, we may speak of a potentially systemic disease of the vessels for the extension and manifestations of which some additional factors are apparently necessary. However, the same may be said of thromboangiitis obliterans where in most cases the disease is limited to the vessels of the lower extremities.

The cause of the disease remains unknown thus far. Some authors have lately been inclined to classify temporal arteritis among the collagen diseases.

The morphological picture of temporal arteritis does indeed resemble the classical form of the collagen disease, periarteritis nodosa. What the various forms of the collagen disease have in common are lesions of the basic sub-

stance of the connective tissue, fibrinoid degeneration of collagenous fibers in combination with necrosis and proliferation on fibroblasts.

Treatment with iodide preparations and penicillin recommended by different authors has not produced any substantial effect. Excision of the affected temporal artery has been observed to relieve headaches in many cases. Some authors have lately described successful results produced by treatment with the adrenocorticotropic hormone and cortisone (Robertson, Whitfield, Cooke, Morin and others). Our first patient began to recover after receiving injections of the adrenocorticotropic hormone. But it did not lead to a rapid recovery. That corresponds to the data obtained in literature according to which treatment with the adrenocorticotropic hormone, or cortisone, leads to a considerable improvement. A relapse may occur after the treatment is interrupted, but it is not as severe as the first attack of the disease.

ACUTE SYSTEMIC LUPUS ERYTHEMATOSUS

At present almost all the authors classify acute systemic lupus erythematosus among the collagen diseases. Nervous lesions associated with this disorder are determined, just as in the case of periarteritis nodosa, by changes in the mesenchimal tissue, chiefly in the vessels of the central and peripheral nervous systems.

Acute lupus erythematosus was first described as a feverish state with skin eruptions. Subsequent investigations revealed that the disease affects various visceral organs, and especially, the serous membranes, lymphatic glands, kidneys, heart, vessels, the cerebral vessels included.

Lesions of the peripheral nerves are usually not as severe as in the case of periarteritis nodosa, but pain and sensitiveness of peripheral nerves to pressure are very often observed.

Diffuse lesions of collagen of the vascular walls call forth the most diverse symptoms of the central nervous system: epileptic seizures, paralyses, aphasia, psychic disturbances and lesions of the cranial nerves. Epileptic seizures are most often observed. Russell, Haserick and Zucker found convulsive seizures in 15 per cent of 144 cases of acute lupus erythematosus described in literature. Out of 28 patients observed by them, seven had epileptic seizures. In two cases epileptic seizures had occurred before the appearance of symptoms of lupus erythematosus, in three cases—at the culmination of the disorder, and in two—only in the terminal phase of the disease.

Skin eruptions may be preceded not only by epileptic seizures, but by other nervous syndromes as well: choreiform hyperkinesis (Glaser), hemiplegia (Siekert), and myelitis (Siekert and Clarck). A meningeal syndrome is observed in some patients (T. A. Nevzorova and O. M. Vinogradova, Klemperer).

Psychic disturbances are observed rather frequently. Tumulty observed disturbances of this kind in 25 out of 105 patients. Confusional states, disorientation, paranoid and hallucination syndromes were described by T. A. Nevzorova and O. M. Vinogradova.

Oedema of the retina, perivascular exudaton, and, in rarer cases, haemorrhages are found quite frequently in the eyeground.

The cerebrospinal fluid is normal in most cases. Only in some cases slight increases in albumin and mild pleocytocis have been described. Bertrand and Bonnet observed a patient with albuminocytologic dissociation.

The main histopathological change in acute lupus erythematosus is fibrinoid collagen necrosis. The latter is combined with insignificant inflammation localised in small, but numerous nodes. Lesions of the small arteries and arterioles in the form of subintimal fibrinoid collagenous necrosis which spreads among the muscular fibers and also be-

tween the muscular and adventitial coats are found in the brain. Destruction of muscular and connective tissue elements leads to necrosis of the vascular wall and to the obliteration of the lumen in consequence of endothelial proliferation. Small infiltrations composed of mononuclear and polynuclear cells are observed around the vessel. (Fig. 16.)

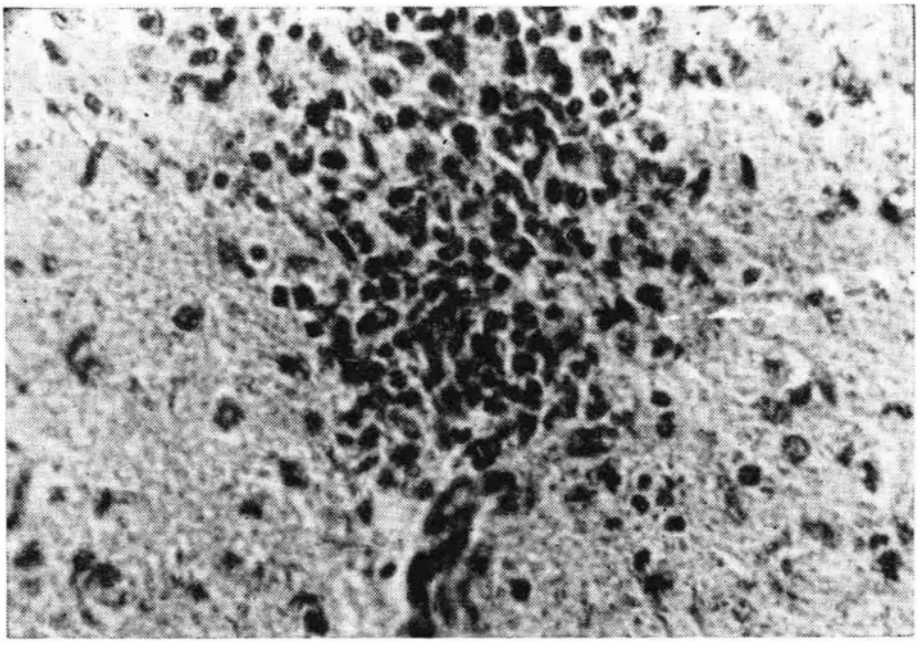

Fig. 16 Acute lupus erythematosus. A node of lymphocytes, histiocytes and glia cells in the white cerebral substance

As a consequence of these processes, the development of more or less diffuse patches of cerebral softening, petechial haemorrhages, and subarachnoic haemorrhages, are observed in some cases.

Glaser and Malamud found numerous small scars in the cerebral cortex which create a picture of granular atrophy. Each of these scars is a consequence of a microinfarction in the grey substance with a reactive gliosis. The white cerebral substance is affected in rarer cases. These changes

in the cerebral cortex could explain frequent epileptic seizures in lupus erythematosus. It should be emphasised that in many cases pathological changes of the cerebral vessels do not produce any clinical symptoms.

The course of the disease is in general unfavourable, remissions being observed only in some cases. Peripheral nervous symptoms may improve, while symptoms of the central nervous system are less susceptible to remissions. The prognosis of the disease is poorer in cases where symptoms of cerebral lesions are evident.

The diagnosis rests largely upon skin eruptions, but they may not appear in some cases. It is most important to detect L. E. cells in the blood which are rarely found in other diseases.

Lupus erythematosus is treated at present with hormonal preparations (cortisone, prednisone). This treatment leads to more or less protracted remissions in some cases. In most cases, however, the disease keeps on progressing and leads to a fatal outcome.

TAKAYUSU SYNDROME (PULSELESS DISEASE, OR AORTIC ARCH SYNDROME)

Takayusu's syndrome is a rare disease conditioned by the obliteration of the main arteries which branch out from the aorta. Accordingly, the pulse in the carotid artery brachial and radial arteries is drastically weakened, or altogether absent, the arterial pressure is greatly lowered and in pronounced cases it cannot be measured. On the other hand, the pulse in the lower extremities is well palpable and the arterial pressure there may even be higher than usual.

The patients complain of weakness and paresthesia in the upper extremities, attacks of giddiness and dimness of vision. Loss of consciousness, may also be observed, especially due to abrupt changes in the position of the head, and attacks of weakness in the masseteric muscles. A sys-

tolic and diastolic bruit may be heard in some patients at the base of the neck. Acute development of collateral blood circulation may cause destructions in the ribs.

An insufficient blood supply to the upper part of the trunk brings on characteristic changes in the eyeground: the arteries are contracted, their caliber uneven, the veins are dilated and varicose, and haemorrhages into the retina are evident in some cases. An atrophy of the iris and cataracts can be observed in some patients.

Cerebral lesions are expressed in epileptic seizures, permanent or transient paresis of extremities, attacks of speech disturbances, hemianopsia.

We refer to our own observation.

Patient X., age 30, was brought to the neurological department on May 25, 1959 with complaints of weakness and limited movements of the left extremities, giddiness and dimmed vision when the head is bent forward.

Considers herself ill since March 1955 when a feeling of general weakness appeared, the temperature rose to 37.6-37.8° C and erythrocyte sedimentation to 32 mm per hour. Two months later pain appeared in the right arm under physical strain and the absence of pulsation was observed on the dextral radial artery. In the end of 1955, she was treated at a hospital whence she was discharged with the diagnosis of septic endocarditis.

In January 1956, pain appeared in the left hand also under physical stress and pulsation disappeared in the sinistral radial artery. Beginning with April attacks of giddiness and dimness of vision began to appear, at times combined with a loss of consciousness when the head was inclined forward.

The patient received a course of treatment with cortisone, whereupon her condition improved, her faints ceased to recur and the temperature returned to normal, the rate of erythrocyte sedimentation remaining high.

On December 19, 1958, a feeling of weakness appeared suddenly in the sinistral extremities. It increased on the following day, and when the patient tried to get up she fell down; a complete paralysis of the left arm and leg set in. Subsequently, she began to regain her movements gradually and began to move independently.

At the examination the patient was found to possess a proportioned physique and satisfactory nutrition. Consciousness clear. Heart boundaries normal, tones clear, distinct, the first sound slightly

amplified. A faint systolic bruit heard deep in the fovea jugularis. The pulse in the radial, brachial, temporal and carotid arteries on both sides not palpable. The pulse in the posterior artery of the foot rhythmic, full, its rate 75 beats per minute. Arterial pressure in the legs 140/90 mm Hg. Pressure in the region of the carotid sinus brings on giddiness and dimness of vision.

The left nasolabial fold flattened. Vaguely expressed sinistral hemiparesis with high tendon reflexes and sinistral Babinski's sign. Hemihypesthesia on the left. Eyeground normal.

Blood count, May 28, 1959: Hb 70%, leukocytes 9,400, eosinophils 4%, segmented cells 74%, lymphocytes 17%, monocytes 5%, erythrocyte sedimentation 38 mm per hour.

In another case, described in detail by Y. D. Smirnov and B. M. Shpilberg, we observed swoons, pain and weakness in the arms and legs, and transient hemiparesis.

The disease has been observed in young and middle-aged women. In most cases it is caused by arteritis of undefined etiology which affects in the first place the muscular coat of the aorta and that of its branches. Cases have been described when the disease was caused by syphilitic aortitis, atheromatosis, chronic dissecting aneurysm of the aorta and traumatic injury of the thorax. Some authors (Hang Hsio-teng, Ch'yu Fu-hsi) are inclined to classify the Takayusu syndrome among the collagen group, considering it a consequence of hyperergic reactions.

In the absence of indications for specific therapy, it is recommended to prescribe cortisone and the adrenocorticotropic hormone. Cases have been described of successful surgical treatment by means of endarteriectomy, or resection and substitution of a nylon membrane for the aortic wall (Warren and Triedman).

Chapter II

LESIONS OF THE NERVOUS SYSTEM ASSOCIATED WITH DISEASES OF THE HAEMOPOIETIC ORGANS AND BLOOD

PERNICIOUS ANAEMIA (ADDISON-BIERMER DISEASE)

The first descriptions of lesions of the spinal cord associated with pernicious anaemia date back to the end of the 19th century (Lichtheim, Minnich and K. M. Birulya). The disease was named funicular myelitis which corresponds to the general ideas accepted at the time when any disorder of the spinal cord, irrespective of its nature, was called myelitis. Later it was proved that inflammatory changes in the spinal cord associated with pernicious anaemia are secondary, reactive symptoms, and preference was therefore given to the name myelosis. A number of synonymous names are used in literature for defining this disorder. French authors use the term "neuro-anaemic syndrome". A term which is widely current in Anglo-American literature is "subacute degeneration of the spinal cord".

According to statistical data quoted by contemporary authors, myelosis is found in most cases of pernicious anaemia. It should be noted that the percentage of spinal lesions in pernicious anaemia given by old and new authors differs sharply. Pappenheim found changes in the nervous system in only six per cent of cases, Taylor in 12 per cent. Recent figures are much larger: 74 per cent according to Wilson, 90-97 per cent according to Meulengracht, 93 per cent according to A. Y. Lovtskaya, and 91

per cent according to our own observations. The figures undoubtedly fluctuate depending upon the thoroughness of the neurological examinations. W. Russel Brain directs attention to the fact that the number of deaths from funicular myelosis in 1933 was doubly greater than in 1927, i.e., prior to the introduction of hepatotherapy. Some authors are inclined to believe that the increase in the incidence of funicular myelosis is explained by the concentration of attention on them and the ability for better diagnosis. Others believe that this increase is due to the use of hepatotherapy which lengthens the life of the patients. If in the past neurological symptoms were disguised by general symptoms which prevailed in the picture of the disease, now that the general condition is improved by hepatotherapy the picture of funicular myelosis becomes more conspicuous.

Clinical symptoms of nervous lesions manifest themselves in most cases only after the appearance of typical changes in the blood and after somatic symptoms become evident in the form of general weakness, changes in the pigmentation of the skin and glossitis. The clinical picture of funicular myelosis rarely appears prior to changes in the blood.

The first symptoms of nervous lesions are paraesthesia in the extremities expressed in numbness, burning, prickling, formication, and, in rare cases, in aching sensations.

In some cases the patients do not attach any importance to subjective sensations for a long time and only anamnestic information makes it clear that they have been affected by paraesthesia for many months. In much rarer cases the disease begins with motor disturbances such as a feeling of fatigue in legs, paresis, disturbed gait.

Combined symptoms of lesions of the posterior and lateral columns of the spinal cord are observed in typical cases of funicular myelosis. Symptoms of lesions of the posterior columns include deep sensorial disturbances, ataxia, disappearance of tendon reflexes. Lesion of the

lateral columns produces weakness in the extremities with increased tendon reflexes, the disappearance of the abdominal and cremasteric reflexes, pathological pyramid signs, increased muscular tone.

Subsequently, paresis of the extremities attains a degree which makes it impossible for the patient to move independently. Spastic paraparesis of the lower extremities are very often succeeded by flaccid paraparesis: tendon reflexes descend or disappear altogether. Sensorial disturbances become more intense; they acquire a conductive character and spread on all forms of sensorium.

Pathological pyramid reflexes remain for a long time in the case of flaccid paralysis with the absence of tendon reflexes. This specific combination of pyramid symptoms and flaccid paresis is characteristic of funicular myelosis.

The upper extremities are affected to a considerably lesser degree. Disturbances here are limited in most cases to sensorial disorders and increase or disappearance of tendon reflexes.

Constipation, imperative and precipitant urination, retention at the beginning of urination are indicative of lesions of the lateral columns, while the distention of the bladder, the presence of residual urine and ischuria paradoxa are consequences of lesions of the posterior columns.

The typical picture of the disease described here is observed in less than 50 per cent of all the cases. Lesions of the posterior columns are characteristic of the majority of cases: lessening or disappearance of tendon reflexes, paraesthesia, and deep sensorial disturbances. In rarer cases we find lesions of the lateral columns only in the form of spastic paraparesis of the lower extremities with pathological pyramid reflexes.

Along with cases in which only initial symptoms are observed in the form of paraesthesia and mild disturbances of deep sensibility, there are cases in which a picture of transverse myelitis is established within 2-3 weeks.

In view of the specific course of the disease in each

case, it is quite difficult to single out some or other forms, or stages, of the disease. In general, it is possible to distinguish the abortive form, syndrome of lesions of the posterior columns, syndrome of lesions of the lateral columns and the combined form of lesions of the posterior and lateral columns.

Psychic changes are observed quite frequently. They may appear before other nervous symptoms have become evident. Ordinarily, high irritability, bad mood and depressive state are observed. Psychic asthenia is often encountered: the patients are apathetic, taciturn, they tire rapidly at the slightest mental effort. Cases of pronounced psychosis in the form of psychomotor excitation, persecutory delusions and states of delirium, are observed more rarely. In these cases psychic changes are apparently caused not by intoxication, but by anatomic lesion of the cerebrum. An indication in favour of this view is afforded by histopathological changes in the cerebral hemispheres similar to the degenerative changes in the spinal cord.

The syndrome of polyneuritis in pernicious anaemia was described by A. Y. Lovtskaya, A. S. Chernikov and S. N. Sharavsky. Atrophy of the muscles of the wrists and feet, the peripheral type of sensorial disorders and the tendency towards relaxation of the gravity of the symptoms may be taken as an inidication of polyneuritis.

Symptoms of atrophy of the ophthalmic nerves in the eyeground are found very rarely. The cerebrospinal fluid is normal. In the overwhelming majority of cases, changes characteristic of pernicious anaemia are found in the blood.

The course of the disease is exceptionally varied. In some cases it progresses slowly, in others—it remains static for a long period of time. In some cases, however, the progress of the disease is rapid and the patient dies of sepsis resulting from ascending urogenic infection, or decubitus. In the absence of treatment, the patients die

most frequently of anaemia itself, or of accidental infections, rather than of nervous lesions.

The pathological picture of funicular myelosis is characterised by disintegration of the myelin sheaths and axis cylinders in the fibers of the white substance of the spinal cord with the formation of vacuoles owing to inadequately reactive proliferations of glia. Small vacuoles ap-

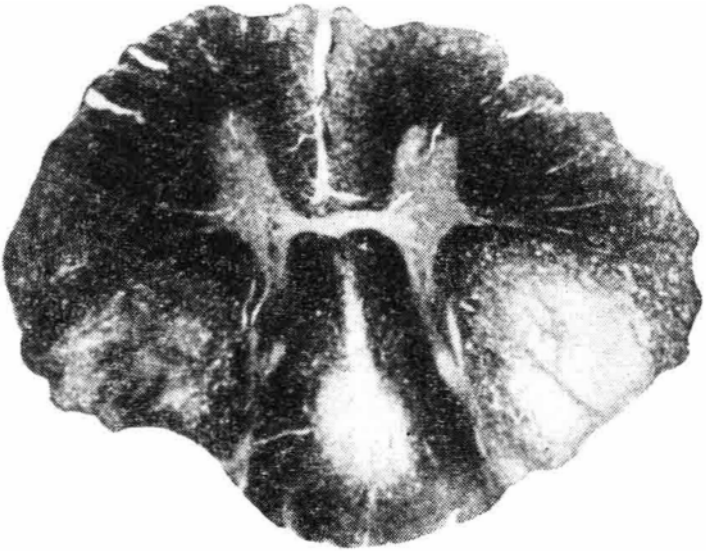

Fig. 17. Funicular myelosis in pernicious anaemia. Degeneration of the posterior and lateral columns

pear in the posterior columns and posterior regions of the lateral columns of the spinal cord at the very beginning of the disease. Gradually the destruction of the white substance with the formation of vacuoles of different sizes spreads over the whole of the spinal cord, leaving in the terminal stages only a narrow zone around the grey substance free from lesions. This may be combined with symptoms of secondary degeneration, chiefly in the cervical region of the spinal cord. These secondary degenerations account for the mild symptoms of sclerosis in the thoracic and cervical parts of the spinal cord. (Fig. 17.)

The process is localised within the separate conductive systems; it does not embrace the entire cross-section, but

spreads to the adjoining bundles, which speaks in favour of a non-systemic disease. On the periphery of the vacuoles it may be seen that the myelin sheaths and axis cylinders are in different stages of disintegration: from simple swelling to complete disappearance. The patholog-

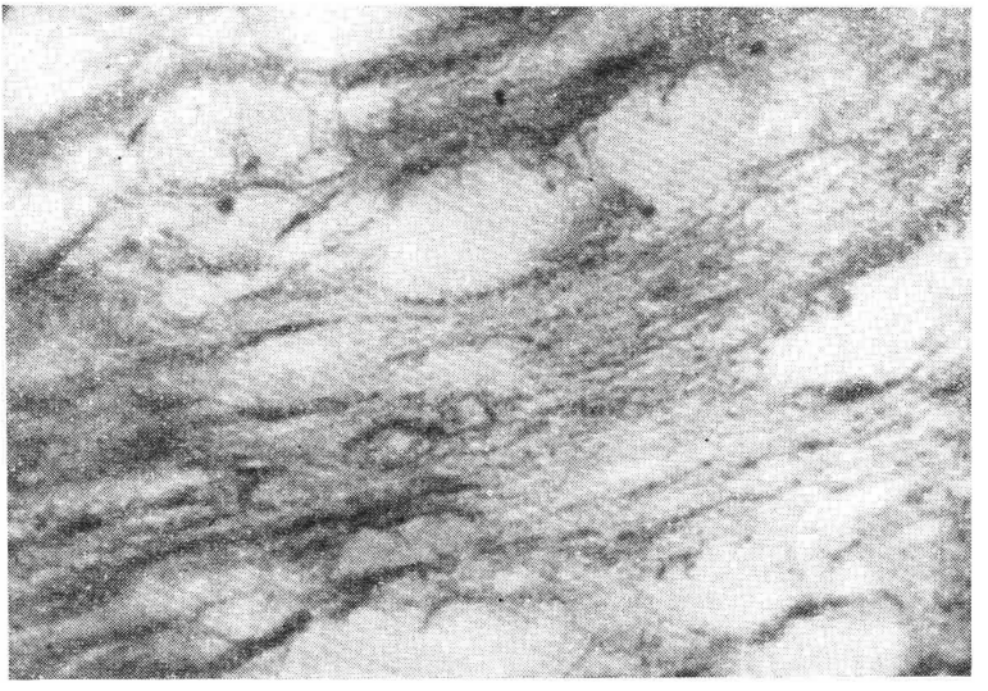

Fig. 18. Funicular myelosis in pernicious anaemia. Formation of vacuoles in posterior columns of the spinal cord

ical process affects chiefly the long spinal tracts and spares the short tracts around the grey substance. In the late stages of the disease the short tracts are also affected, but to a considerably lesser degree. (Fig. 18.)

A characteristic feature is the dissociation between the disintegration of nervous tissue and the glial reaction. In the white substance the vacuoles are very poorly isolated by the formation of gliotic strands. The small number of proliferating astrocytes soon undergo regressive changes. As already pointed out, no signs of sclerosis or of the formation of a gliotic scar are found in the spinal cord, with

the exception of the region of secondary degenerations in the cervical and partially in the thoracic region.

In the region of degeneration the blood vessels are more numerous, their walls are thickened, and hyaline degeneration is observed in some cases. Accumulations of macrophages containing fat and products of lipoid disintegration may be seen around the vessels.

The grey substance of the spinal cord is not affected. The question of changes in the peripheral nervous system has not been adequately investigated. Nonne, Bodechtel and others insist that the peripheral nerves remain intact. Nor have we found any changes of the peripheral nerves in the cases observed by us. Other authors describe degenerative changes of nerves and nerve roots (Van Bogaert, Greenfield and Carmichael).

Pathological changes in the cerebrum are much rarer than in the spinal cord. Typical foci with the disintegration of myeline membranes and áxis cylinders may be found in the white substance of the cerebrum. Microscopic circular haemorrhages which do not differ in the least from similar haemorrhages in cases of intoxication and in other diseases which cause haemorrhagic diathesis are also evident in the cerebrum. Lastly, in some cases diffuse changes of cells are sometimes found in the cerebral hemispheres; they are expressed in tigrolysis, pigmentary degeneration and sometimes even in destruction of cells.

Some authors maintain that changes characteristic of funicular myelosis are observed in other diseases as well. They are described in various forms of anaemia, leukaemia (Kast and Wohlwill), carcinomatosis (Lubarsch and Bertrand), syphilis (M. B. Krol and A. S. Chernikov), avitaminosis (Nonne), Basedow's disease (Schilling, A. N. Matovetsky) and brucellosis (Y. I. Tarakanov).

Consequently, the role of an etiological factor in funicular myelosis is ascribed to the most diverse diseases. M. B. Krol, M. A. Khazanov and I. L. Sosnovik are of the

opinion that various harmful factors which act upon the organism over a long period of time and lead to emaciation, create a predisposition to funicular myelosis. In the last few years, however, there have been increasing objections to this concept.

According to data of contemporary authors and to our own observations, funicular myelosis is found in the overwhelming majority of cases of pernicious anaemia, whereas it is very rare in other emaciating diseases. As for the cases of myelosis without anaemia described in old literature, it should be remembered that owing to shortcomings of the old methods of investigation and to the lack of knowledge about latent forms of anaemia, the etiological factor of funicular myelosis was incorrectly estimated. Examples of this kind have been analysed in detail by A. Y. Lovtskaya. It is known, furthermore that changes in the blood may set in much later than symptoms of funicular myelosis.

Histopathological changes described as funicular myelosis in other diseases include, in addition to the degeneration of the posterior and lateral columns, other changes which are not characteristic of funicular myelosis. Cerebral lesions in carcinomatosis are distinguished by the involvement into the process of the posterior roots and meningeal membranes, diffuse development of the process and acute oedema of the spinal cord. Perivascular infiltrations which are not characteristic to funicular myelosis, nodes of leukaemic cells in the spinal cord and membranes are found in cases of leukosis. Experimental investigations with repeated dehaematisation of animals for the purpose of inducing in the spinal cord changes resembling funicular myelosis, did not produce any favourable results. Nor were any changes characteristic of myelosis produced by anaemia which was induced experimentally by injections of pyridine, glycerin and pyrogallol.

At present all the investigators agree that anaemia itself is not the cause of this disease. This is indicated pri-

marily by the absence of parallelism between the changes in the blood and in the nervous system. Funicular myelosis, just as achylia and glossitis, may precede anaemia. Since the adoption of hepatotherapy for treatment of pernicious anaemia, it has been constantly observed that, despite the restoration of the normal picture of the blood, nervous symptoms may continue to progress. These facts suggest the conclusion that anaemia is not the cause of funicular myelosis, but that the two diseases are caused by a common etiological factor.

Castle has advanced the theory that normal gastric juice contains an "intrinsic" antianaemic factor and that its correlation with the "extrinsic" factor contained in the food, is necessary for erythrocyte maturation, normal haemopoiesis and for the normal functioning of the nervous system. It has now been proved that Vitamin B_{12} is the extrinsic factor. Investigations have shown that an intrinsic factor belongs to the gastromucoproteins. The intrinsic factor enters into an unstable compound with Vitamin B_{12}, extracting it from the food and assisting in its assimilation by the organism. Absence of the intrinsic factor in the organism leads to insufficient assimilation of Vitamin B_{12} from the food.

The absence of parallelism observed frequently between the course of anaemia and funicular myelosis suggested the idea that there was no complete identity between the pathogenesis of anaemia and funicular myelosis. Latest investigations have revealed different reactions to folic acid in cases of anaemia and funicular myelosis. Folic acid, taken orally, leads to a rapid remission in pernicious anaemia, but it does not prevent the appearance of funicular myelosis and does not arrest its development (G. A. Alexeyev).

Some authors explain the incapacity of folic acid to relieve nervous symptoms by the fact that it synthesises desoxyribonucleic acid and unlike Vitamin B_{12} it does not

take part in the formation of ribonucleic acid. This question is being studied at present.

Experimental investigations conducted by S. I. Yakovlev, V. N. Chernigovsky and D. I. Goldberg have shown that disturbances in the innervation of the stomach in dogs leads to marked reduction or complete disappearance of the intrinsic factor from the gastric juice. These investigations point to the role of trophic functions of the nervous system in the pathogenesis of the disease.

It is not difficult to make a *differential diagnosis* in cases when the patient suffering from pernicious anaemia develops symptoms of nervous lesions. It is much more difficult to diagnose a case when the patient applies to a doctor for the first time with complaints of nervous symptoms, or when nervous symptoms precede changes in the blood. The real cause of pain and paraesthesia in the extremities may be overlooked at first and ascribed to atherosclerosis of the cerebral blood vessels, polyneuritis or endarteritis of the vessels of the extremities. In cases of inadequately expressed changes in the blood, a differential diagnosis should be made between tabes dorsalis, multiple sclerosis and syphilis of the spinal cord.

Unlike atherosclerosis, paraesthesia in the case of funicular myelosis is more protracted and intense and it is associated with objective sensorial disturbances. In general, when paraesthesia is observed in persons over 40 years of age, accurate blood tests should be made which may suddenly disclose the real cause of the disease. Discovery of atrophy of the mucuous membrane of the tongue and achlorhydria, is of value for the diagnosis.

In the case of endarteritis the pulse on the arteries of the extremities is faint or completely absent and the colouring of the toes is changed, while oedema or pastiness of the feet is characteristic of funicular myelosis. Funicular myelosis, as distinct from tabes dorsalis, is character-

ised by pyramid symptoms; that is indicative of involvement of the lateral columns of the spinal cord into the process.

In cases when only symptoms of lesions of the posterior columns are evident the absence of changes in the pupils, normal cerebrospinal fluid and negative Wassermann's reaction are indicative against tabes dorsalis. Syphilis of the spinal cord is accompanied by early disorders of urination, symptoms of cranial nerve lesions, positive Wassermann's reaction and changes in the cerebrospinal fluid.

Unlike multiple sclerosis, funicular myelosis is not accompanied by atrophy of the temporal section of the ophthalmic nerves, scanning speech and nystagmus. Tremor of the extremities is observed rarely and is not of an intentional character. A fact which speaks against multiple sclerosis is the development of the disease in old age, the combination of the simultaneous disappearance of tendon reflexes and pathological reflexes and the beginning of the disorder with paraesthesia. In funicular myelosis, paresis are much more pronounced than pyramid symptoms owing to the patient's general weakness, and the patients cease to move independently much earlier than in multiple sclerosis. Blood and gastric juice tests are of decisive importance in unclear cases.

Amyotrophic lateral sclerosis is excluded owing to the presence of muscular atrophies, bulbar symptoms, absence of paraesthesia and sensorial disorders.

In cases of tumours of the spinal cord the disturbances are not limited to the posterior and lateral columns, and albuminocytologic dissociation in the cerebrospinal fluid is indicative against funicular myelosis.

Pernicious anaemia and cancer usually affect people of the same age group. Cachexia and secondary anaemia in cancer may complicate the differential diagnosis. Moreover, weakened deep and vibratory sensibility, as well as weakened tendon reflexes, may be observed in elderly

people. Therefore, if achylia is observed in elderly people, all the necessary examinations for excluding cancer should be made.

The results of treatment with hepatic preparations are not as effective in funicular myelosis as it is observed in relation to somatic symptoms of pernicious anaemia. That is explained by the fact that the blood composition is permanently restored, while restoration of nervous tissue does not take place in the brain; therefore, in far advanced disintegrations it is impossible to expect the complete rehabilitation of a function.

Davison made histopathological examinations of the spinal cord of seven patients who were treated with hepatotherapy and of 10 patients who did not receive this treatment. The picture of changes in the myelin and axis cylinders was similar in both cases. In all cases where hepatotherapy was employed, gliotic scars were found which were not observed in the untreated cases. In Davison's opinion these investigations show that as the result of the rapid formation of a gliotic scar hepatotherapy arrests the development of the process. He believes that liver weakens the toxic action of the pathogenic factor and thus strengthens the capacity of glia for reactive proliferation. In one of our patients who received treatment with liver the tendency towards the formation of gliotic scars was clearly pronounced, while in two other patients this tendency was not observed.

The success of treatment of funicular myelosis with liver and hepatic preparations (campolonum, antianaeminum) is due to a number of factors: the early beginning of treatment, prescription of bigger doses than in pernicious anaemia, and, lastly, by long and systematic administration of the mentioned preparations.

Experience has shown that in funicular myelosis the effect produced by Vitamin B_{12} is greater than that of hepatotherapy. The feeling of weakness, giddiness, paraesthesia and pain in the extremities disappear within 5-7

days. Good results have also been obtained in the initial stage of acute paraplegia. Especially noteworthy is the effect produced by treatment begun not later than three months after the appearance of symptoms of funicular myelosis. Timely, protracted and repeated treatment with Vitamin B_{12} prevents the appearance of nervous symptoms, improves the existing objective picture and arrests the progress of funicular myelosis.

One of our patients, who had been ailing for two years and had lost the capacity for independent movement two months before he was brought to the hospital, regained the ability to move independently, without a crutch, two weeks after the beginning of treatment with Vitamin B_{12}. But the pyramid symptoms did not disappear.

Vitamin B_{12} therapy should be employed over a long period of time. A daily dose of 100-200 γ of vitamin injected intramuscularly over a period of two weeks, is followed by injections of 50 twice a week over a period of six months and then by 50 γ once in two weeks. The dosage should be individualised and, if necessary, increased.

ERYTHRAEMIA (POLYCYTHAEMIA)

Cases of polycythaemia associated with different organic disorders of the cerebrum were described long ago: encephalitis (A. M. Geimanovich), narcolepsy (Lhermitte, Peyre), disorders of the diencephalon (Da Rin, Costa); some of the latest descriptions deal with polycythaemia observed in cases of cerebellar angioreticuloma (Y. V. Shmidt). Carpenter, Schwartz and Walker observed two cases of cerebellar haemangioblastoma with polycythaemia which disappeared after the removal of the tumour.

Nervous changes in cases of true polycythaemia are observed frequently. In the very first description of this disease Vaquez (1892) directed attention to the significance of nervous lesions.

In eight out of every ten cases of polycythaemia the patients complain of more or less marked headaches, giddiness, tinnitus, a feeling of fever, fatigue and poor sleep. Headaches are constant, accompanied by a feeling of fever and heaviness in the head. In some cases these headaches resemble attacks of migraine with vomiting, and/or scotoma. The giddiness may be systemic and accompanied by tinnitus.

Patients often complain of high fatigability, irrascibility and lack of working capacity. Flaccidity, apathy, slow speech, memory failure, drowsiness and depression are often observed. In the case described by R. A. Tkachov, nine days before the patient's death the state of drowsiness and general weakness was succeeded by psychomotor excitation, disorder of orientation and delusions. All the neurotic and psychic symptoms may completely disappear if the blood composition is normalised.

Dilatations, tortuousness and cyanosis of the retinal veins are observed in the eyeground; thrombosis of these veins, haemorrhages, scotomas and paroxysmal dimness are found in rarer cases, and blindness, diplopia and nystagmus are still rarer. Papilloedema was observed in some of our patients, along with other symptoms of high intracranial pressure, such as headaches, vomiting, high tension of the cerebrospinal fluid. In the case described by Christian, the intracranial pressure syndrome in combination with symptoms of focal lesions in the cerebrum suggested the diagnosis of a tumour and a performance of craniotomy.

Symptoms of focal lesions of the brain usually appear in far advanced stages of the disease, but disturbances in the cerebral blood circulation may also be among the initial symptoms of the disease. Hemiparesis and hemiplegia, aphasia and hemianaesthesia are observed most frequently. Cerebrovascular accidents are often bilaterial, and may occur repeatedly. They are caused most frequently by thrombosis of the cerebral arteries. Our following obser-

vation may serve as an illustration of multiple secondary softenings in the brain in cases of polycythaemia.

Patient S., age 57, was admitted to the hospital on December 2, 1956 with grave disorders of speech.

The anamnesis was compiled on the basis of the information given by her husband. Headaches which appeared in 1953 led to the discovery of an elevated arterial pressure. Acute disturbances of speech which occurred in 1954 lasted for a week. In September 1956, the patient became aware of weakness and stiffness in the right leg. In October, she was overtaken suddenly by attacks of vomiting and drastic weakness in the right extremities. Subsequently the patient's condition took a turn for the worse; she ceased to understand speech, and urination incontinence was added to these symptoms. On November 15, she was placed in City Hospital No. 56 whence she was transferred on December 2 to the neurological department of City Hospital No. 4.

At the time of admission the skin of the face was a deep red, the wrists and feet—cyanotic. The condition was grave. Nutrition of physique low, decubitus in the region of the buttocks. In the lungs emphysematic signs, vesicular, weak breathing. Heart boundaries dilatated moderately leftwards, sounds dull, arterial pressure 150/100 mm Hg. Tongue coated, abdomen somewhat rigid. Liver and spleen unpalpable.

Nervous symptoms: Sensorial and motor aphasia. Dextral hemiplegia with high muscular tone of the right extremities of the spastic type. Tendon reflexes high, mainly on the right. Babinski's sign on the right.

Blood count: Hb 108%, erythrocytes 8,870,000, blood quotient 0.8, leukocytes 9,800, band cells 8%, neutrophils 59%, lymphocytes 28%, monocytes 5%, erythrocyte sedimentation 6 mm per hour. Prothrombin time 30 seconds. Prothrombin index 80%. Urine: albumin 0.6‰, leukocytes 7-10 in the field of vision, erythrocytes—2-3 in the field of vision.

The condition was growing worse, the temperature rose to 38.8° C., disturbances of respiration appeared and the patient died on January 2, 1957.

Clinical diagnosis: Polycythaemia of the Vaquez-Osler type, multiple patches of cerebral softening with the main focus in the basin of the left mid-cerebral artery, oedema of the lungs.

Anatomical diagnosis: Polycythaemia (the Vaquez-Osler disease), splenomegaly, red metaplasia of the marrow of the femoral bones, multiple patches of cerebral softening, thrombosis in the branches of the pulmonary artery and infarction of the lower lobe of the left lung, dystrophic changes of the myocardium, liver and kidneys.

Intracerebral and subarachnoic haemorrhages and thrombosis of cerebral veins are observed not as frequently as thrombosis of the cerebral arteries.

Of special interest in polycythaemia is erythromelalgia. It is characterised by severe pain in the extremities, hyperaemia and profuse perspiration. Pain is localised mainly in the lower extremities, frequently in the big toe, and is of a pricking, burning nature. It grows in intensity when the patient is standing or walking, and is accompanied by vasomotor disturbances expressed in reddening of the skin, perspiration and local rises in temperature. In some cases, each deterioration of the blood picture is accompanied by simultaneous deterioration of erythromelalgic symptoms.

Three stages may be singled out in the development of erythromelalgia. The first stage is associated with the appearance of paraesthesia, pain and cyanosis of the big toe. Subsequently the pain extends to the knee, and sometimes over the whole extremity, and haematomas appear under the skin. Ulceration of the toes begins in the last stage. In one of the cases observed by us, erythromelalgia was the first symptom of polycythaemia which made the patient apply to a doctor. Cases have been described when pain in the legs bore the nature of intermittent claudication. In rare cases an amputation is required owing to the development of gangrene.

Nervous lesions in polycythaemia are distinguished by great polymorphism, but the following basic syndromes may be singled out in the picture of the disease: high intracranial pressure syndrome, vasocerebral lesions syndrome, the syndrome of erythromelalgia and syndrome of psychic asthenia.

Pathological anatomy. Drastic plethoria of the meningeal and cerebral vessels is observed in polycythaemia. Small patches of softening are often found in great numbers, chiefly in the white substance. Haemorrhages into the brain, and thrombosis of the cerebral sinuses are

found in fewer cases. Descriptions are available of diffuse meningeal infiltrations by erythrocytes, saturation of the soft membranes and cortex by haematogenous pigment and hydrocephalus. In most cases the cerebral vessels are unchanged but they are plethoric. In addition to glial proliferation and perivascular infiltration with lymphocytes, unevenness of the lumen of the capillaries and minor vessels with saccate distentions were observed in Winter's case. Winkelman and Berns found turgescence and endothelial proliferation of the minor vessels, with obliteration of the lumen in some cases. In the ganglion cells they found changes resembling those in anoxaemia.

Pathogenesis of nervous symptoms in polycythaemia is determined in the main by circulatory disturbances. Kety's investigations have shown that a very decelerated blood flow is observed in the cerebrum in polycythaemia. The increase in the blood mass, its saturation with cellular elements and increased viscosity tend to decelerate the blood flow and lead to the formation of stasis, obliteration of the capillaries with subsequent disturbances in the blood supply of the cerebral tissue, and the appearance of necrotic nodules. Disturbances of the blood flow may also produce diapedetic haemorrhages. Hyperthrombocytosis, along with hyperviscosity, is an important factor in the pathogenesis of thrombosis in erythraemia. The clinical picture of polycythaemia abounds in periodic attacks of migraine, giddiness, transitory blindness and rapidly passing paresis. All these rapidly disappearing symptoms cannot be explained by stasis and obliteration of blood vessels only. We are edivently dealing with vasomotor disturbances based on functional disturbances of vascular innervation. An increase in the blood mass and its hyperviscosity play an important part in the pathogenesis of erythromelalgia. Vascular turgescence and blood repletion stimulate the nerve ends which cause vascular spasm, stasis and consequent thrombosis.

There is no great difficulty in *diagnosing* polycythaemia,

if its possibility is not forgotten, especially in cases where vasocerebral disorders are combined with a characteristic hyperaemia of the face and mucous membranes, with enlargement of the liver and spleen. Increases in the number of erythrocytes and other cellular elements of the blood confirm the diagnosis. When disturbances of the cerebral blood circulation occur in young and middle-aged people, the possibility of polycythaemia should be remembered, along with syphylis, cardiac insufficiency and renal diseases. Polycythaemia may also produce syndromes of neurasthenia, atherosclerosis, hypertensive disease and high intracranial pressure. It should be emphasised that in some cases the patient's face does not exhibit the characteristic redness and only a repeated blood test may therefore become the decisive diagnostic factor in polycythaemia. Erythraemia (polycythaemia) as an independent disorder should be distinguished from various types of erythrocytosis which may be observed in different diseases: pulmonary emphysema, congenital heart diseases, Cushing's disease, etc. Should cerebellar symptoms or signs of high intracranial pressure be observed, the possibility of angioreticuloma of the cerebellum should be excluded.

LEUKOSIS

The first clinical observation of nervous lesions in leukaemia date back to 1811, when Burns gave in his *Observations on the Surgical Anatomy of the Head and Neck* what was apparently the first description of chloroleukaemia. Symptoms of diplopia, impaired vision in the left eye, exophthalmos, and at the same time, a tumour appearing from the temporal bone were observed in a young man. Multiple green tumours were found at the post mortem in the cranial bones, dura mater, lacrimal gland and accessory sinuses of the nose. According to contemporary data, nervous lesions are observed in 25 per cent of the patients

suffering from leukosis. M. P. Khokhlova found nervous symptoms in 32 out of 139 patients suffering from this disease.

Numerous localisations and variety of causes which involve the nervous system into the pathological process in cases of leukosis, create an exceptional polymorphism of neurological symptoms. When symptoms of nervous lesions dominate in the picture of the disease, the latter may resemble an acute infectional disease of the nervous system, or a tumour. More frequently, however, nervous symptoms are found after the somatic symptoms of the disease become adequately clear.

Leukaemic infiltrations in the organs do not develop metastatically, but appear as the result of local proliferation from undifferentiated mesenchymal tissue. Reacting by proliferation, just as in the other organs, the mesenchymal tissue in the nervous system causes compression of the nervous tissue. The speed with which the clinical picture of nervous lesions develops depends upon whether the disorder is acute or chronic. In some cases leukaemia takes the form of a vascular disorder, which is due to haemorrhagic diathesis, or rarer, to the penetration of the vessels by white blood elements. A noteworthy fact is the frequent absence of parallelism between the intensity of anatomic changes and the pronounced character of the clinical symptoms. In several cases we found leukaemic infiltrations which produced no clinical symptoms at all.

In many cases, the development and course of the nervous symptoms are not parallel to the nature and course of the basic process. In chronic leukaemia infiltration spreads to the mesenchymal tissue of different organs in consecutive order, the nervous system being involved only with the generalisation of the process. In such cases nervous symptoms enter gradually into the existing clinical picture of leukaemia. In other chronic cases the basic process is associated with rapidly developing nervous symp-

toms in consequence of vascular, haemorrhagic and thrombotic processes.

This variety corresponds to the polymorphic character of the clinical picture: neuralgia and paralysis of the peripheral nerves, meningeal symptoms, syndrome of acute myelitis, compression syndrome, Landry's syndrome, haemorrhages into the brain.

In acute leukaemia, the rapid development of nervous symptoms disguises by its gravity other symptoms of the disease. The following observation may serve as an illustration.

Patient G., age 47, was admitted to the hospital on September 27, 1952. At the age of 22 had acute rheumatism; does not remember having had any other diseases. Intense pain in the lumbar region felt from time to time during the past year.

Intense lumbar pain and weakness in the legs appeared on November 8. General weakness and paresis of the legs progressed rapidly, and ten days later the patient could no longer move independently.

The patient is emaciated, the skin and mucous membranes faintly coloured, the gums flabby and bleeding. A big bundle of enlarged, painful lymphatic glands palpable in the dextral armpit, painful exostosis at the crest of the sinistral ilium. Lungs normal. Heart boundaries normal, tone dull. Abdomen flatulent, liver and spleen not palpable. Temperature 36.7-36.9° C. Reaction of pupils to light brisk. Paralysis of all branches of the dextral facial nerve. Remaining craniocerebral nerves normal. Volume and strength of arm movements normal. Paresis of the lower extremities most expressed in feet and toes. Patellar and brachial reflexes high. Achilles tendon and abdominal reflexes could not be elicited. Pathological reflexes absent. Sensitiveness to pressure along nerve endings. Bilateral Lasegue's and Kernig's signs. Decreased peripheral sensoriums in distal parts of the extremities. Sphincter functions preserved.

Blood count: Hb 42%, erythrocytes 3,200,000, leukocytes 148,000, basophiles 2%, eosinophils 7%, myeloblasts 22%, promyelocytes 8%, myelocytes 15%, juvenile forms 12%, band cells 8%, segmented cells 20%, lymphocytes 3%, monocytes 3%.

Urine: Gravity 1,015, albumin 0.16‰, leukocytes 10-12, hyaline cast 1-2 within the field of vision.

In the next few days the patient's condition took a sharp turn

for the worse. The temperature rose to 38-39° C. Blood appeared in the feces and urine. Difficult breathing. Patellar reflexes faded away. Urine retention. Occipital rigidity. Kernig's sign. Patient died on the eighth day of his stay at the hospital.

Clinical diagnosis: Acute myeloid leukaemia, Landry's syndrome.

Anatomical diagnosis: Acute myeloid leukaemia, hyperplasia of the spleen, haemorrhagic diathesis, fibrinous pneumonia, parenchymatous degeneration of the heart.

Microscopic study: The sternum marrow composed predominantly of myeloid cells; the same picture observed in the femoral marrow. Considerable clusters of myeloid cells, mainly myelocytes, along the capillaries in the liver, with occasional megacaryocytes. Positive reaction to oxidase. Clearly pronounced myeloid hyperplasia of the pulp in the spleen. Myeloid hyperplasia with positive reaction to oxidase in the lymphatic glands.

Nervous system: Macroscopic examination revealed a haemorrhage with a range of 2×3 cm observed in the right cerebellar hemisphere. Hyperplasia and infiltration of pial membranes in the region of the cerebral stem and cerebellum. The minor vessels are filled with myeloid cells. Spinal cord in cervical and thoracic regions normal in transection. Spinal cord softened from II lumbar segment downwards, its pattern in transection vague. Pial membranes sharply thickened at the level of the thoracic and of the lumbar region especially.

No changes found in either hemisphere or in the cerebral stem. Pial membranes in the lumbar region of the spinal cord sharply thickened, lost their normal structure and consist entirely of myeloid elements enveloping in a muff the spinal cord, the anterior and posterior root endings. The dura mater infiltrated by the same cellular elements along the edge adjoining the pial membrane. Blood vessels are heavily static, numerous capillaries, barely discernable in norma, are evident; they are packed with myelocytes (positive reaction to oxidase). Hyalinosis of vascular walls. Cellular infiltrations do not penetrate into the substance of the spinal cord, with the exception of the sulcus intermedius anterior where they extend along the vessels. The pial membranes in the thoracic region are also infiltrated by myeloid elements, but here they do not seem like a solid granulated mass. In the lumbar region of the spinal cord ischemic necrotic sections in the white substance shaped like triangles, their base turned towards the periphery of the spinal cord. Nerve cells are distended into vesicular shape, diffusely stained. Anterior and posterior roots degenerated, and their interstitial tissue also drastically infiltrated in many places. Both facial nerves diffusely infiltrated by myeloid elements. The cells distributed mainly

in the perineural spaces, but found also between separate fibers. Perineural infiltration by myeloid cells observed also in some sections of the ischiatic and femoral nerves.

There are descriptions of cases of leukosis with engorged papillae (M. B. Tsuker), cerebrovascular accidents and hemiplegia (Lasser) and Jacksonian epilepsy.

Compression paraplegia is sometimes observed in consequence of the pressure of epidural infiltrations upon the spinal cord. The initial symptom is just as in the above-described case: pain in the back accompanied by sensitiveness of the vertebra to percussion and tension of the longissima muscles of the back. This period of stimulation of the nerve endings is succeeded by the phase of progressive compression of the spinal cord, with paraparesis, segmental sensorial degeneration and sphincter disorders. The disorder may be mistaken for a tumour of the spinal cord. There are descriptions of cases when laminectomy was performed (Critchley, Greenfield).

Hamburger describes five cases of myeloid leukaemia which resembled a vascular disorder. The post mortem revealed changes in the spinal cord caused partially by "red" and partially by "white" stasis, which led to the penetration of the myelin tissue chiefly by myeloid elements with secondary disturbances (proliferation) of the vascular wall.

Dam Peter described a case of a generalised herpes zoster in lymphatic leukaemia. The post mortem revealed a diffuse infiltration of the posterior nerve roots by lymphatic cells, as well as their perivascular infiltration of the vessels of the pial membrane of the spinal cord (the intervertebral ganglia were not examined). The author reports 22 cases of the combination of a herpetic girdle and leukaemia collected in literature and believes the latter to be a factor predisposing to the herpes zoster. It should be noted that the herpetic girdle is described also in cases of lymphogranulomatosis, lymphosarcoma, multiple mye-

lomatosis and metastasis of cancer in the spinal column. Goldman is of the opinion that the herpetic symptom appears before the compression of the spinal cord. The author recommends preventive *X*-ray treatment of the corresponding region of the spinal cord if herpes appears. In our two cases, however, the herpetic eruption was not followed by symptoms of compression of the spinal cord. It is quite probable that by involving the intervertebral ganglia in the process of above-mentioned diseases activate a latent virus.

Peripheral paralysis of the facial nerve has been observed along with symptoms on the one part of the spinal cord (L. M. Dukhovnikova). Fried, who in 1926 collected in literature 30 cases of nervous lesions associated with leukaemia, directs attention to lesions of the cranial nerves in seven cases and to bilateral paralysis of the facial nerves in four out of seven cases. In the years that followed similar cases were described by Trömner and Wohlwill. In the case of Garvey and Lawrence, bilateral paralysis of the facial nerve was the only symptom of the involvement of the nervous system in the process.

Cranial nerves are affected more often than the spinal nerves. In one of our cases of chronic lymphatic leukaemia, the patient developed paraesthesia, pain and weakness in the arms and legs. An examination revealed the absence of the patellar and Achilles reflexes and sensorial disorder of the peripheral type. N. A. Goldenberg described two cases of acute leukosis the clinical picture of which resembled polyneuritis. An autopsy performed 12 weeks after the appearance of the initial symptoms of the disease revealed a typical picture of leukaemia, and a histopathological examination brought out a leukocytal infiltration of the peripheral nerves. In the author's opinion, polyneuritis was caused not by infiltration, but by a specific leukaemic toxin.

There are a few indications concerning the nature of the changes in the cerebrospinal fluid. An examination of

the cerebrospinal fluid in two of our cases revealed an albuminocytologic dissociation, and in one case pleocytosis was observed (48 lymphocytes in 1 mm^3) along with a hyperalbuminosis.

Hyperalbuminosis is caused not only by compression of the spinal cord, but also by the fact that the flow of liquor in the perineural spaces of the nerve roots is blocked by infiltrations, as well as by the exudation of albumin from the dilated vessels in which the blood flow is in a state of prestasis, or stasis.

Diagnosis. Consequently, exceptionally varied as the clinical picture of nervous lesions is in leukaemia, there is not a single nervous symptom pathognomonic for this disorder. The way to a correct diagnosis in doubtful cases is a thorough clinical examination of the patient, and, primarily, a morphological blood test, marrow puncture and myelographic study.

It should, however, be borne in mind that the picture of the blood is quite often not very typical, or remains unchanged. In such cases the basis for a diagnosis may be furnished by the existing enlargement of the lymphatic glands, rapidly progressing emaciation, high temperature, haemorrhages into the skin, or retina, nasal and renal haemorrhages, painfulness of the ribs and sternum to pressure, enlargement of liver and spleen. In doubtful cases of organic lesions of the nervous system concomitant with the given symptoms, the possibility of leukaemia should be considered.

Pathology. As already mentioned here, the great variability of the clinical picture of nervous lesions in cases of leukosis is due not only to the numerous localisations of the process, but even more so to the differing character of the changes in the nervous tissue.

The main histological feature is the infiltration of various parts of the nervous system by myeloid cellular elements, and by the proliferation of leukomas in the epidural cellular tissue. The latter is observed most frequently

in cases of chloroleukaemia; 17 cases of spinal lesions collected in literature by Chritchley and Greenfield, included 12 cases of chloroleukaemia. (Fig. 19.)

In one of the cases observed by us, leukaemic green-stained masses extended in a solid ring around the dura mater, and only in isolated sections were the pial mem-

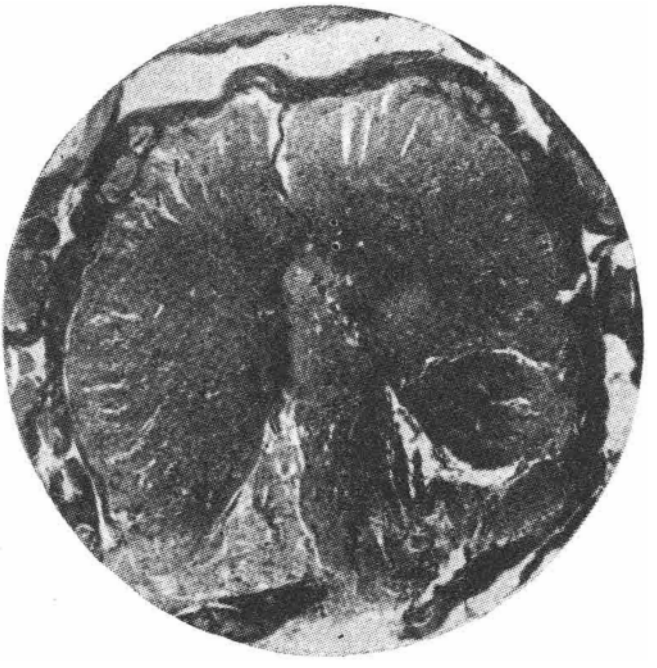

Fig. 19. Myeloid leukaemia. Pronounced thickening of the pial membrane infiltrated by myeloid cells

branes infiltrated. In some cases, this infiltration of the epidural cellular tissue was so insignificant that it could not cause compression of the spinal cord. The membranes and their vessels were infiltrated to a greater or lesser degree by myeloid cells in all cases. In one patient, the pial membranes were actually steeped in myeloid cells causing a drastic thickening of these membranes, which was evident even in the macroscopic examination. Infiltration of the III and VII pairs of cranial nerves was observed in the same case. In two other cases infiltrations were ob-

served in the examined spinal nerves; they were located in the perineural spaces and between separate fibers. (Fig. 20 and 21.)

Infiltration with myeloid cells of the spinal and cerebral substance is observed much rarer. In such cases the infiltrations are located around the vessels and they are

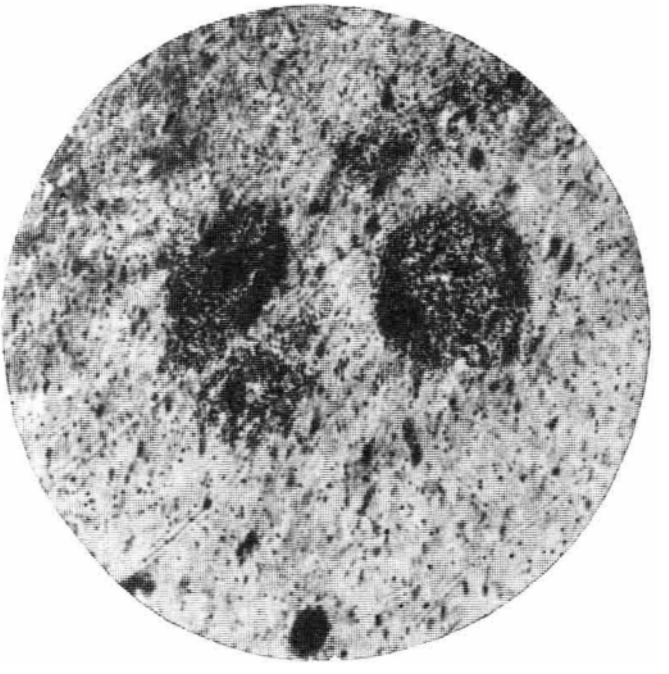

Fig 20. Myeloid leukaemia. Medulla oblongata. Perivascular infiltration by myeloid elements

often surrounded by haemorrhages of various sizes. We have observed patches of softening in the spinal cord. These necrotic patches were caused by circulatory disturbances in the vessels of the meningeal membranes and cerebral tissue. Clottage of vessels by leukaemic cells leads to thrombosis with subsequent softening of cerebral tissue. (Fig. 20.)

Cerebral haemorrhages serve as one of the manifestations of haemorrhagic diathesis which complicates the course of leukaemia. Haemorrhages of this kind, which pre-

sent a clinical picture of a cerebrovascular accident or subarachnoid haemorrhage, are well known. Some authors believe that haemorrhages of this type lead to blood effusions into the white cerebral substance only and that they are often multiple ones and are distinctly separated from the surrounding tissue. There is a description of a case of

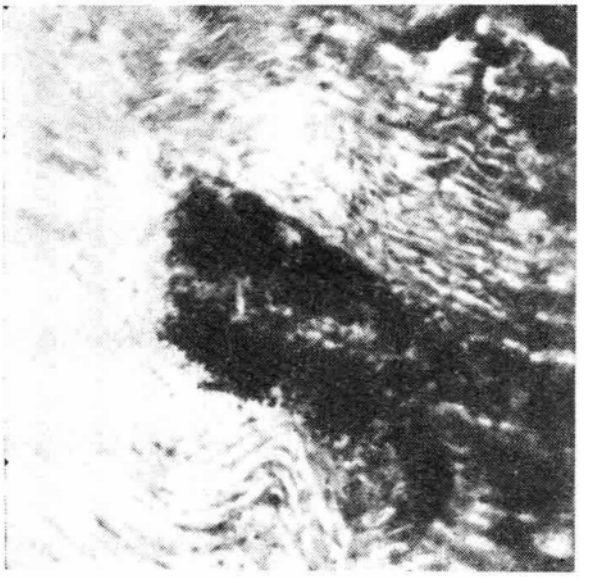

Fig. 21. Lymphatic leukaemia. Focus of infiltration by lymphatic cells in the ischiatic nerve

myeloid leukaemia with hemiplegia resulting from the clottage of a vessel by myeloid elements. In one case we found a blood effusion into the white substance of the cerebellum which was not diagnosed during the patient's life. Along with erythrocytes, accumulations of myeloid cells were found in the focus of the haemorrhage.

Authors who believe that funicular myelosis may be observed in leukaemia refer to observations described long ago by Nonne, Schultze and Müller. It should be noted, however, that in these cases, with pronounced sclerosis in the posterior columns and small vacuoles, the myelin

disintegration typical of funicular myelosis was not observed in the lateral columns. In our observations, the foci of white substance degeneration differed from the changes in funicular myelosis by a smaller number of vacuoles which showed no tendency for fusion. They are characterised by diffuse location, their clusters extending in the main transversally along the lateral columns. Unlike funicular myelosis, the proliferative glial reaction is distinctly expressed here. Had these changes constituted an early stage of funicular myelosis, as some authors believe, then in advanced cases typical changes could have been expected, but no descriptions of this kind are available to this day. Moreover, in leukaemia the foci of disintegrated tissue are connected with the distribution of the vessels.

According to our observations and literary data different histopathological pictures in the most diverse combinations may be found in the same case of leukosis. These changes may be classified as follows:

1) vascular lesions causing thrombosis, softening and haemorrhages;

2) infiltration by myeloid cells of the nerves, roots, membranes and substance of the spinal cord and cerebrum;

3) proliferation of leukomas in the epidural tissue with subsequent compression of the spinal cord;

4) reactive changes of cells, fibers and glia.

This explains to a certain extent the discrepancy between the chronic course of the leukaemic process and rapid development of nervous symptoms. Nervous symptoms are produced in these cases not by leukaemic infiltration, but by vascular changes the development of which resembles cerebrovascular accidents. It is noteworthy that in many cases the clinical picture does not correspond to the intensity of the anatomical changes. Wohlwill and Trömner found in 10 out of 12 cases of leukaemia infiltrations which were not expressed clinically. Only in seven out of 14 cases described by Diamond were the

losses of nerve cells observed, moreover not all of them were affected by severe lesions.

This accords with the opinion entertained by some authors that, in spite of extensive infiltrations, vitally important organs remain functionally intact, in cases of chronic leukaemia: although the liver has been enlarged for many years, no symptoms of hepatic insufficiency are found; there is no sign of residual nitrogen or uraemia, notwithstanding the infiltration of both kidneys. Perhaps in cases such as our case, when the histological picture is reduced to infiltration by leukaemic elements, an additional toxic factor is necessary for the development of polyneuritis. The strict symmetry of the lesion is another indication of this.

Involvement of the nervous system in acute leukaemia aggravates the prognosis and often leads to rapid death, which usually occurs from a cerebral haemorrhage.

LYMPHOGRANULOMATOSIS

Sternberg, who described the histological picture of lymphogranulomatosis in 1899, put forward a hypothesis that the unusual localisation of lymphogranulomatosis would become all the more usual the more frequent both macroscopic and microscopic examinations of the organs are made. This is true also in relation to the nervous system. In the first description of the disease, in 1832, Hodgkin reported that the process, which had spread to the lymphatic glands of the neck, axilla, bronchial tubes, groin and mesenteric lymphatic glands, penetrated the pial membranes and infiltrated them. Ginsburg found nervous lesions in 27.7 per cent of all the cases of lymphogranulomatosis observed by him.

The spinal cord and its nerve roots are affected most often in lymphogranulomatosis. The course of the disease resembles that of a tumour of the spinal cord, or spondy-

litis with gradually progressive paresis and sensorial conductive disturbances. In some cases, paralysis of the extremities appear suddenly.

Nervous lesions appear in most cases after an extensive affection of the lymphatic glands and visceral organs by lymphogranulomatosis. Cases have been observed of paraplegia developing ten years after the appearance of the first symptoms of lymphogranulomatosis.

There are, however, descriptions of many cases where isolated lymphogranulomatic nodes were removed as an extramedullary tumour, the true nature of it being revealed only by a histological examination.

In one of the cases observed by us, lesions of the spinal cord developed in the final stage of lymphogranulomatosis, five years after the appearance of the initial symptoms of the disease. A complete paraplegia developed overnight. This type of sudden paralysis, without any prodromal symptoms, could be explained only by acute myelomalacia caused by obliteration of the vascular lumen by lymphogranulomatous masses.

Albuminocytologic dissociation, (and sometimes xantochromia) are found in the spinal fluid, in a picture of compression of the spinal cord. Queckenstedt's test also brings out distinct symptoms of a subarachnoid block. In the case described by Urechia and Goia, when lymphogranulomatous formations penetrated the pial membranes, the fluid contained 58 lymphocytes, and in B. Y. Serebryanik's case—360 lymphocites in 1 $mm.^3$ Nevertheless, a mild pleocytosis may also be observed without granulomatic penetration of the subarachnoid space. In one of our cases, when the lymphogranulomatous process did not penetrate the pial membranes, we found 12 lymphocytes in 1 $mm.^3$ Apparently, mild pleocytosis may be caused by reaction of the membranes to necrotic processes precipitated in the spinal cord by pressure.

Pain in the extremities often observed in lymphogranulomatosis is caused by pressure of enlarged lymphatic glands

upon the nerves and plexuses. This pain bears the character of persistent neuralgic and neuritic pain. Herpes is observed when intervertebral ganglia are infiltrated.

Lesions of the cranial nerves are observed in some cases. Paraf and others described cases of paralysis of the oculomotor nerves. Mate observed a bilateral paralysis of the facial nerve. We have observed lesions of the trigeminal nerve. N. V. Konovalov and O. A. Khondarian observed paralysis of the trigeminal, auditory and facial nerves. Paralysis of the diaphragm may appear suddenly and then disappear with the diminution of the ganglia which press upon the n. phrenicus.

Peripheral nerves are affected not only as the result of pressure by lymphogranulomatous nodes, but also in consequence of general intoxication. We have observed a patient who developed polyneuritis after a course of X-ray therapy, during the reverse development of the lymphogranulomatic process. In another of our observations—a case where the the picture of polyneuritis had been progressing for six months, an X-ray examination of the chest revealed lymphogranulomatic proliferations in the mediastinum and in the lungs. It is possible that the cause of these polyneuritic processes lies not in any specific change, but in the toxic action of products of albuminous disintegration released in great amounts, especially in the reverse development of granuloma. The mechanism of nervous lesions in this case may resemble tuberculous polyneuritis which also is of a toxic, rather than of a specific nature.

Symptoms of cerebral lesions are much rarer than lesions of the spinal cord and peripheral nerves. Epileptic seizures of the general (Ginsburg, Aszkanasi, Hecker and Fischer), or of the Jacksonian type, may be observed in the syndrome of high intracranial pressure. Focal cerebral symptoms are very rare. Headaches, vomiting, sinistral ptosis, diplopia, paresis of the lower extremities with deep sensorial disturbances were observed in B. Y. Serebrya-

nik's case. Very pronounced meningeal symptoms and psychic changes appeared several months later. The disease was diagnosed as an atypical form of tubercular meningitis and tubercular peritonitis. The autopsy revealed lymphogranulomatosis of the mesenteric lymphatic glands,

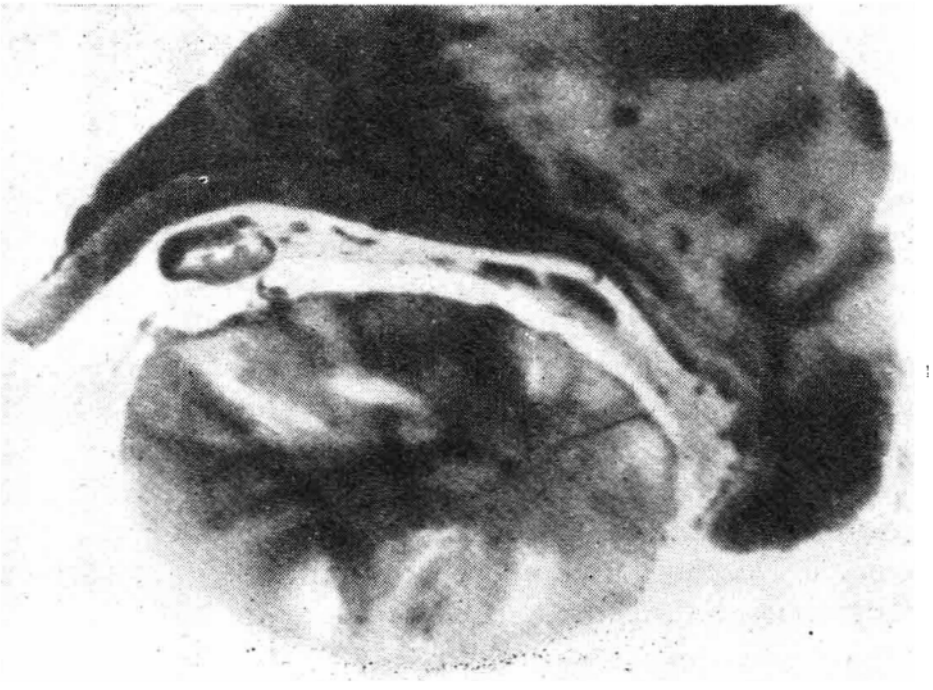

Fig. 22. Lymphogranulomatosis. Lymphogranuloma in the epidural cellular tissue. Compression and softening of spinal cord

intestinal walls, the cerebrum with its pial membranes, the abducens and auditory nerves, the gasserian ganglion, the intervertebral ganglia and, partially, of the spinal nerve roots.

Pathology. Pathological changes in lymphogranulomatosis may be divided into specific and non-specific ones. The latter are caused by compression of nervous tissue and circulatory disturbances. Most often com-

pression of the spinal cord is caused by lymphogranulomatous nodes which penetrate into the vertebral canal. (Figs. 22 and 23.)

In autopsies observed by us lymphogranulomatous formations were located in epidural cellular tissue and were

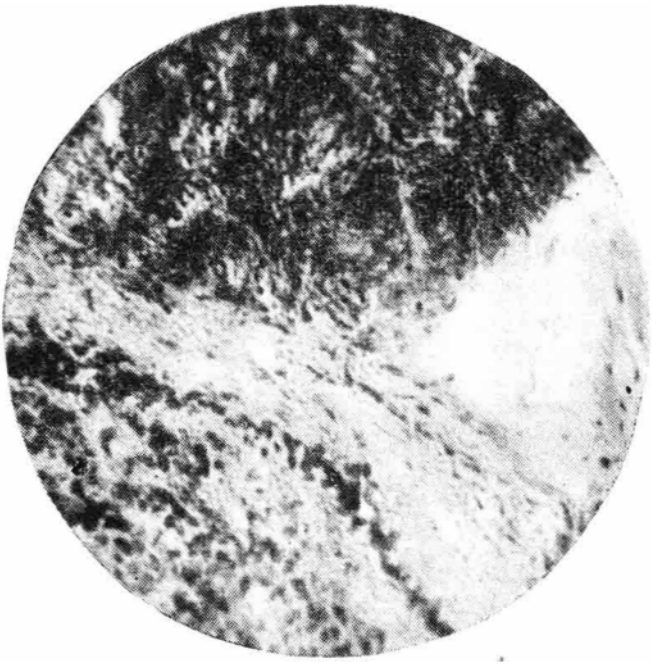

Fig. 23. Lymphogranulomatosis. Lymphogranulomatous proliferation of the exterior strata of the dura mater

composed of typical granulation tissue with histiocytes, giant cells, lymphocytes and eosinophils. In one case lymphogranuloma penetrated into the vertebral canal directly from affected vertebra, in two other cases lymphogranulomas in the epidural cellular tissue were not connected with the vertebral process. The dura mater is quite a stable barrier which arrests the subsequent development of the process. In two cases, infiltration by polymorphous cells was evident only in the external strata of the dura

mater, while the deeper strata were not affected. In the third case a deeper infiltration of the dura mater was found, but even here the infiltration did not reach the inner surface of the membrane. According to most authors, granulation tissue does not penetrare beyond the dura mater. It was found in the pial membranes by Walthard, Ure-

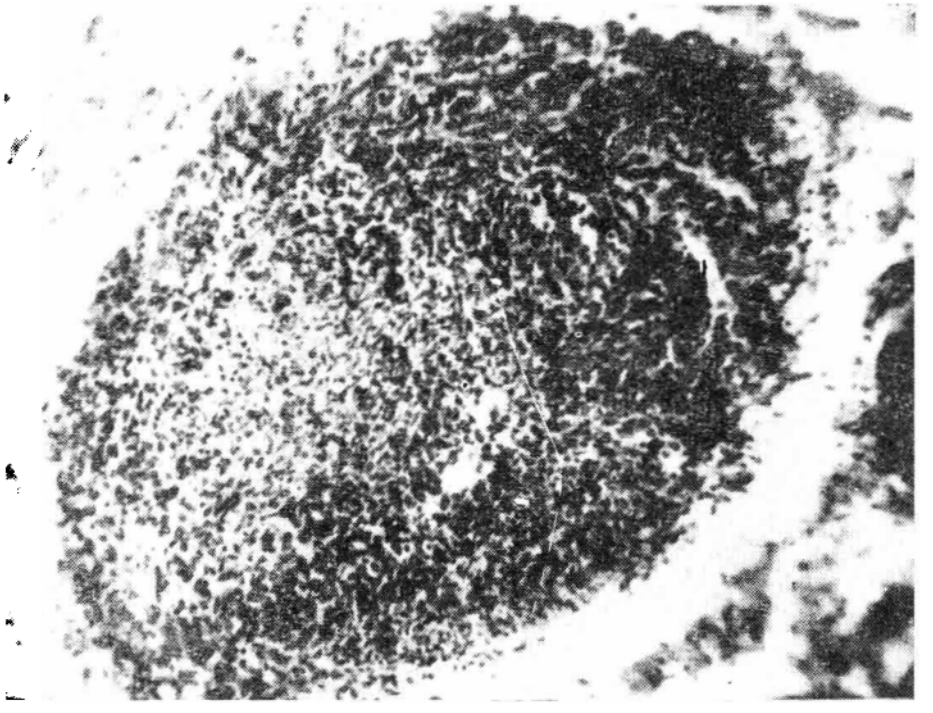

Fig. 24. Lymphogranulomatosis. Lymphogranulomatous proliferation of the trigeminal nerve root

chia and Goia, N. V. Konovalov and O. A. Khondkarian, and others.

Specific changes in the spinal cord were found by Urechia, Goia and others. Goia discovered a lymphogranuloma in the posterior columns. Hecker and Fischer found lymphogranulomatous nodes in the white matter of the cerebrum. There were cases when one lymphogranulomatous node was found in the cerebellum and another—in the occipital lobe. (Fig. 24.)

In the case of diabetes insipidus described by Sternberg, a typical granuloma was found in the diencephalon. Környey describes a lymphocytic perivascular infiltration around the III ventricle, the sylviduct and infundibulum, but does not consider it specific for lymphogranulomatosis. It is noteworthy that no Berezovsky-Sternberg cells were found in the infiltrations in almost all the mentioned cases. In B. Y. Serebryanik's case, in addition to lesions of the membranes, nerve roots and cranial nerves, numerous perivascular infiltrations were found in the pons, striatum and white substance of the cerebral convolutions. Isolated foci in the striatum were not connected with the vessels. Berezovsky-Sternberg cells were found in them, just as in other parts.

Non-specific changes in the nervous system are caused by pressure of lymphogranulomatous nodes located in adjoining tissues upon the spinal cord and the cerebrum, and by circulatory disturbances conditioned by blocking the vessels supplying blood to the cerebrum and spinal cord. Compression is caused in some cases by lesion of the vertebral column with subsequent sequestration, or displacement of vertebrae. Most often, compression is caused by lymphogranulomatous penetration of the epidural cellular tissue. Myelomalacia is conditioned not only by direct pressure of lymphogranuloma, but also by its blocking of the vessels which supply blood to the spinal cord. Frequent softening of the sternal segments becomes understandable if it is remembered that the blood flow supplying this region passes through the spinal branches of the intercostal arteries which are often blocked by enlarged mediastinal and thoracic lymphatic glands. Walthard described a patch of softening in the spinal cord extending in the shape of a pencil from C_7 to D_3. A histopathological examination revealed that the anterior cerebral artery was blocked by lymphogranulomatous cells.

As for degenerative changes in the white substance, their origin is analogous to that in leukosis. In lymphogran-

ulomatosis, the vacuoles show no tendency towards confluence and the formation of extensive vacuosities. Furthermore, here the vacuosities extend across the transection of the white substance, whereas in funicular myelosis degenerative changes extend to the lateral and posterior columns in the region of the long pathways.

Diagnosis. It is not difficult to make a differential diagnosis in cases when nervous lesions appear simultaneously with other symptoms of lymphogranulomatosis. Considerable difficulty is encountered in cases when other symptoms are vague, atypical, or when they appear later than the nervous symptoms. There was a case when we underestimated a small enlargement of the lymphatic glands, as well as the general emaciation of the patient and weakness which appeared six months before the initial symptoms of paraparesis. The disorder was mistakenly diagnosed as a tumour of the spinal cord complicated by ascending infection of the urinary tract.

There are descriptions of cases when isolated nodes in the epidural cellular tissue were removed as an extramedullary tumour, and only a histological examination revealed the real nature of the tumour. A thorough investigation made in these cases brought to light symptoms of a general disorder which were overlooked earlier or misinterpreted (Ginsburg). Cases of this type were described by Aszkanasi, Hecker and Fischer, and Walthard.

An interesting case of primary lymphogranulomatosis of the epidural cellular tissue was observed by Taylor. The patient, 26 years of age, without any symptoms of lymphogranulomatosis, developed within eight weeks a picture of compression myelitis on the level of the cervical segments. Laminectomy was performed and a 10 cm long extradural tumour removed. A histological examination of the tumour revealed unexpectedly a typical lymphogranuloma. Enlargement of the lymphatic glands appeared six weeks later and the patient died a year after that, despite roentgenotherapy.

The disorder is often confused with tuberculosis of the vertebral column. This mistake is due to the fact that the two processes often affect the same organs: the lymphatic glands and the vertebral column, causing similar reactions in the organism.

Stiffness of the vertebral column, pain in percussion of the spinous processes and pain caused by change of posture, which is especially pronounced in cases when granuloma affects the vertebrae, are sometimes observed. In other cases, *X*-ray examinations reveal destruction of the spongy substance while the intervertebral cartilages remain intact. In other cases, severe sclerosis converts the spongy tissue into "ivory", and the opaque "marble" vertebrum stands out conspicuously also in the *X*-ray picture. The X-ray picture suggests the idea of cancer rather than of tuberculosis. Paravertebral granulomatous formations may resemble a cold tuberculous abscess.

A differential diagnosis with a tumour of the spinal cord is, as we have already pointed out, considerably complicated, if the other symptoms of the disease are not clear. In this case, the diagnosis should be based on general symptoms rather than on neurological signs. At any rate, in case of nervous lesions of unclear etiology it is necessary to bear in mind the possibility of this disorder as well, especially if nervous symptoms are combined with lesions of other organs (abdominal organs, lymphatic glands, the spinal column), itching, perspiration, progressive emaciation and anaemia. A blood test is of relative importance, inasmuch as there are many cases without leukocytosis, eosinophilia and monocytosis. A biopsy or lymphatic puncture make it possible to concretise the diagnosis, but they too are not of decisive value.

Roentgenotherapy produced no effect in our cases, although in literature we find descriptions of cases where considerable remissions were produced by roentgenotherapy. In a case observed by Ginsburg, a patient suffering from paraplegia regained his capacity for moving inde-

pendently. In Luce's case, symptoms of paresis disappeared in all the extremities after X-ray treatment. Lifshits mentions a case of paraplegia of the lower extremities and urinary disturbance; after a course of treatment with roentgenotherapy the patient began to move independently and the urinary disorders disappeared. X-ray therapy of the left hemisphere relieved the patient of epileptic seizures in Ginsburg's case. Unfortunately, this is usually a temporary remission, followed by a relapse within a longer or shorter space of time.

It should be remembered that lymphogranulomatosis often begins as a general disorder with an unfavourable prognosis, the symptoms receding into the background and roentgenotherapy producing no results. Most of the authors agree that there is little indication for surgical interference in the case of lymphogranulomatosis; nevertheless, in the case where an isolated node is responsible for compression of the spinal cord, an operation may lead to a considerable improvement in the spinal symptoms. Cases of this kind were described by S. S. Yudin, Goldman, Tarlov and Gertz, and others. The combination of surgery with roentgenotherapy is especially indicated.

HAEMORRHAGIC DIATHESIS

Haemorrhagic diathesis embraces a group of disorders of varying etiology and pathogenesis but with a common symptom, a predisposition to haemorrhages which often affect the nervous system as well. Blood effusions into the cerebrum and meningeal membranes are described in hemophilia, Werlhof's disease and aplastic anaemia (Roger and Olmer). We had the occasion to observe 10 patients with different types of haemorrhagic diathesis who were brought to the hospital with severe lesions of the nervous system.

Cerebral haemorrhages accompanying essential thrombocytopenic purpura (Werlhof's disease) range from mul-

tiple punctuate effusions to severe focal haemorrhages. Subarachnoid and subdural haemorrhages are encountered almost as frequently as cerebral haemorrhages.

In most cases nervous lesions appear suddenly. A blood effusion into the brain brings on a coma, hemiplegia and other symptoms of focal lesions of the brain. In much rarer cases, hemiplegia, aphasia and sensorial disturbances develop gradually, within 3-5 days. A subarachnoid haemorrhage leads to the rapid development of the meningeal syndrome.

One of our patients was brought to the hospital with Jacksonian epilepsy which developed after a subarachnoic blood effusion. Haemorrhage into the brain are not always of an apoplectic character. In some cases they develop latently, manifesting themselves only in headaches, occipital rigidity and Kernig's sign.

Haemorrhage into the retina are quite frequent and often occur when no symptoms of nervous lesions are evident. Haemorrhage into the spinal cord and peripheral nerves are observed much rarer. Oppenheim described a case in which haematomyelia was brought on by the patient's attempt to break a stick with his foot. (Fig. 25.)

Mild injuries of the extremities may condition blood effusions into the peripheral nerves. We observed a case of haemophilia where, without any obvious injury, haemorrhage took place almost simultaneously into the region of the left shoulder and left thigh, with resulting compression of the ulnar and ischiatic nerves and a distinct clinical picture of the lesion of these nerves. There are descriptions of cases of paralysis of various peripheral nerves in consequence of blood effusions (Lord, Frenkel, Weil). Patients with these symptoms should be placed primarily under the observation of a neurologist. The following two cases may serve as an illustration.

The first patient was brought to the neurological department with the syndrome of severe, acute ischias. The drastic pallor of the patient prompted us to make a detailed

blood test which revealed a typical picture of haemophilia. The pain along the ischiatic nerve was caused by a haemorrhage into the gluteal muscles which pressed upon the ischiatic nerve.

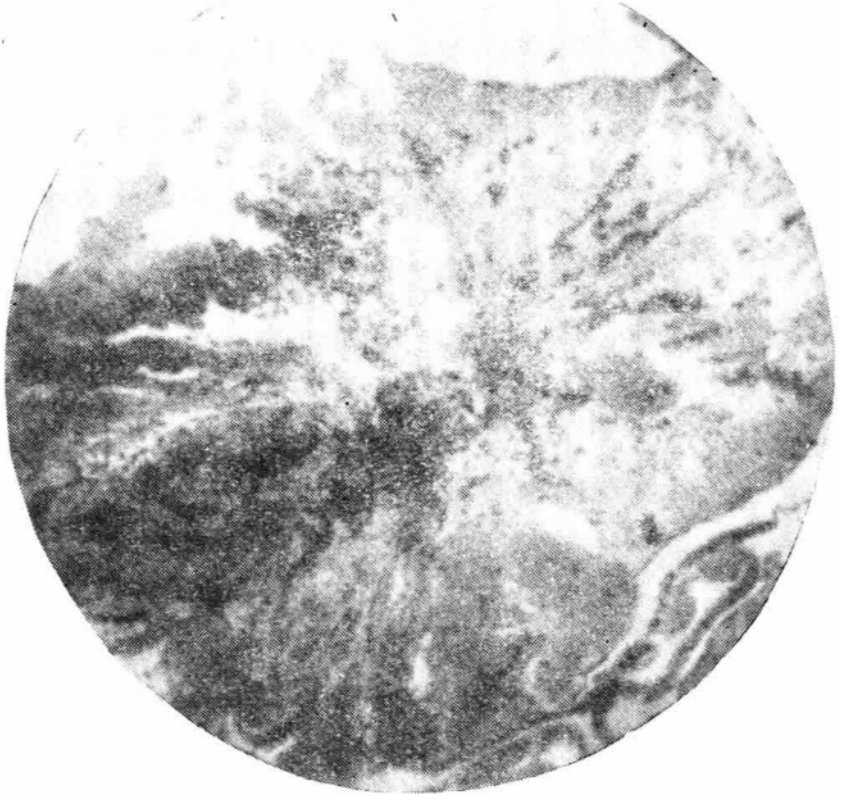

Fig. 25. Haemophilia. Multiple haemorrhages into the spinal cord

The other case was an acute paralysis of the group of peroneal muscles. Purpura of the skin combined with the blood test left no doubt that we had before us a picture of Werlhof's disease.

Pathological anatomy. There is nothing specific in the blood effusions into the nervous system in haemorrhagic diathesis. Histological examinations have not brought out any specific changes in the cerebral vessels. Old patches

of softening and nodules of glial proliferation are found in the brain in some cases. Small blood effusions may not produce any clinical symptoms and only an autopsy may disclose them in the form of punctuate haemorrhages in the cerebral substance or membranes.

The *pathogenesis* of blood effusions into the central nervous system is the same as in the case of blood effusions into other organs. The pathogenesis of peripheral lesions may vary. In some cases, compression of a nerve and its paralysis may be caused by a haematoma near the nerve. Most frequently, the paralysis sets in some time after the appearance of the haematoma. As for the cases when nervous lesions appear suddenly without accompanying haematomas, consideration should be given to the possibility of an interstitial blood effusion into a nerve with consequent constricture and distention of its fibers.

A *diagnosis* is facilitated if the personal and family anamnesis, as well as the pathological picture of the blood, make it possible to recognise the nature of the disorder. In isolated cases haemorrhagic diathesis develops latently; the haemorrhages into the brain and its membranes may resemble a primary nervous disorder. In cases of cerebral haemorrhages and blood effusions into the membranes, especially in young patients, haemorrhagic diathesis should be given consideration along with other causes.

The prognosis in cases of haemorrhages into the brain is always serious, but we have had the occasion to observe a rapid improvement after an operation for splenectomy.

MULTIPLE MYELOMA (RUSTITSKY'S AND KAHLER'S DISEASE)

The disease is marked by tumour-like hyperplasia of the bone marrow. Some authors believe it to be a systemic lesion of the haemopoietic organs, although the majority of specialists classify it among the true tumours. A myeloma may be composed of myelocytes, myeloblasts, plasma cells,

lymphocytes and erythroblasts. Myeloma may be composed of mixed cells and is often multiple. In most cases it is localised in the bones of the chest, ribs, sternum, and also in the pelvic, vertebral and cranial bones.

Patients suffering from myeloma are placed primarily under the observation of neurologists, inasmuch as pain (ossalgia) is most conspicuous in the picture of the disease. O. A. Khondkarian observed 11 patients suffering from myeloma. Most of these patients were brought to the neurological department in connection with nerve root pain. It is a tormenting pain, which deprives the patients of sleep, and not infrequently of the possibility of the slightest movement in bed; it is localised most frequently in the pelvis, in the sacrum along the vertebral column and in the lower extremities. It may sometimes be a diffuse pain. The bones (ribs and sternum) are highly sensitive to pressure. When spontaneous fractures occur, which are quite frequent, an acute localised pain may come on suddenly, more often in the region of a rib, or in the back. A slight rise in the temperature may often be observed. It is usually associated with progressive anaemia and hyperproteinaemia.

The growing tumour may penetrate beyond the bone and involve in the process adjoining tissues, including the nervous tissue. This is followed by severe headaches, paralysis of the cranial and spinal nerves.

Vertebral lesions lead frequently to compression of the spinal cord and to the appearance of paraplegia, which is most frequently flaccid with the disappearance of tendon reflexes, dimunition of the muscular tone and conductive sensorial disturbances. Paraplegia ordinarily develops rather acutely, within several days, in some cases. Albuminocytologic dissociation is found in such cases in the cerebrospinal fluid.

In some cases (L. Y. Pines and L. A. Pirogova, Nonne), complications of the nervous system cannot be explained by the compression of the nervous tissue by a myeloma; they are apparently caused by the action of toxic factors,

such as Bence Jones protein. O. A. Khondkarian believes that changes in the spinal cord are in the main a result of progressive anaemia.

The diagnosis is made on the basis of the general clinical picture (lesions of the bones, anaemia, hyperproteinaemia, peculiar lesions of the kidneys, etc.). Of great importance are the results of roentgenological examinations. X-ray pictures of the affected bones show numerous circumscribed defects, their diameter ranging from several millimetres to 1-3 cm; their edges are distinctly outlined. Bence Jones protein is usually found in the urine, but not in all cases. The diagnosis is finally confirmed when a puncture of the sternum marrow reveals the presence of typical myeloma cells.

In most cases, the prognosis is unfavourable. S. A. Reinberg believes that roentgenotherapy produces different effects which cannot be anticipated in advance. The larger the foci and the fewer their number, the better the results. He emphasises especially the analgesic effect of roentgenotherapy, pointing out that in the case of vertebral fractures this treatment, as a rule, improves the neurological picture.

SARCOIDOSIS (BESNIER-BOECK'S AND SCHAUMANN'S DISEASE)

Sarcoidosis is a systemic disorder of a "benign" lymphogranulomatous type. I. V. Davydovsky believes that sarcoidosis may be classified among the reticuloendotheliosis group. It is a chronic disorder where skin, lymphatic glands, salivary glands, lungs and bones are affected. Soft nodules, ranging from one to several centimetres in size, are formed in the derma. Enlargement of the lymphatic, submaxillary and parotid glands is often observed. The picture in the lungs resembles miliary tuberculosis. X-ray pictures show small cysts in the fingers and toes. Enlargement of the salivary glands and uveoparotitis are observed in some cases.

Nervous lesions are rare in sarcoidosis, but it is important to know them because they may result in the patient's rapid death.

Most frequently observed are bilateral paralysis of the facial nerves which often occur in combination with parotitis, but do not depend upon the latter because they frequently appear even before the development of parotitis. There are also descriptions of neuritis and atrophy of the ophthalmic nerves, lesions of the oculomotor nerves, of the IX-XI pair of cranial nerves and auditory disturbances.

Paralysis of cranial nerves are combined in some cases with lesions of peripheral spinal nerves (separate nerves can be involved, or a picture of polyneuritis may develop). This may be concomitant with muscular paralysis of the extremities and with sensorial and reflective disturbances.

The central nervous system is involved into the process rarely; more than 60 cases of cerebral lesions associated with sarcoidosis are described in literature. The intracranial pressure syndrome (pseudotumour) and chronic optochiasmal arachnoiditis are most frequent. Pennell (1951) notes that diabetes insipidus was observed in 18 and the adiposogenital syndrome in five out of 51 cases described in literature.

General Jacksonian epileptic seizures, hemiplegia, aphasia, hemianopsy and psychic disturbances have also been described. Lesions of the spinal cord and of the medulla oblongata may assume the character of a degenerative disorder, or tumour.

In some cases the course of the disorder resembles diffuse meningitis with occipital rigidity and Kernig's and Brudzinski's signs. Changes in the cerebrospinal fluid (high content of albumin, mild pleocytosis and decreased sugar content) are observed in 50 per cent of the cases of nervous lesions associated with sarcoidosis.

Consequently, the clinical picture of the nervous system is distinguished by exceptional variety and depends upon the region involved in the pathological process.

Two types of lesions are brought out by the pathological examination. The first type, diffuse granulomatous meningitis, is localised most frequently in the region of the diencephalic funnel, hypophysis and at the fundus of the III ventricle; moreover, the granulomas do not penetrate the cerebral substance, but they cause compression of the cranial nerves and chiasm, atrophy of the ophthalmic nerves, as well as hydrocephalus with symptoms of high in-

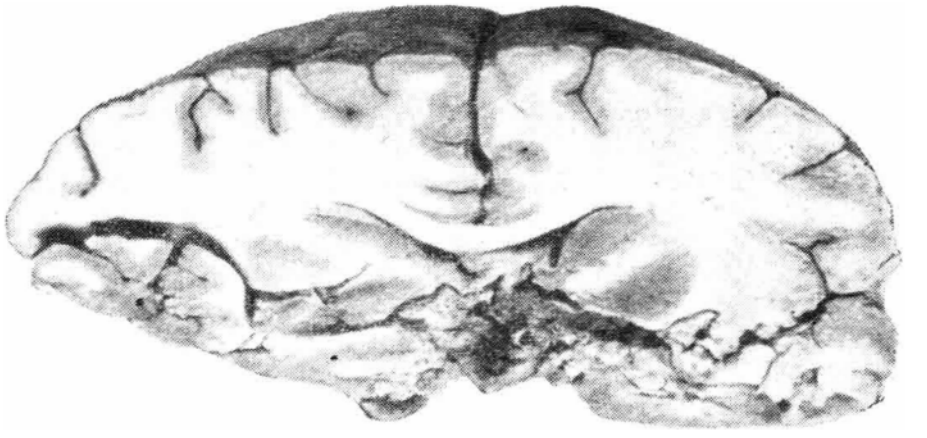

Fig. 26. Sarcoidosis. Sarcoid granulomas in the region of the hypothalamus

tracranial pressure. In the second type, the granulomas are more limited; they are small-sized and are located in the cerebral substance. Microscopic studies have revealed colonies of epithelioid cells with small numbers of giant cells in the cerebral substance and membranes as well as in other organs. Clusters of lymphocytes are evident along the edges of the epithelioid islets. Sarcoidosis is sharply distinguished from tuberculosis by the absence of caseous necrosis. (Fig. 26.)

The etiology of sarcoidosis remains unknown to this day. There are three hypothesis. According to one of these the disorder is conditioned by tuberculosis; the second ascribes the origin of sarcoidosis to an independent as yet undiscovered infectious agent. Facts have recently been cited in

favour of the hypothesis that this disorder is a peculiar hyperergic syndrome which may be brought on by different causes. Should this hypothesis prove to be correct, it will be possible to classify sarcoidosis among the group of collagen disorders, just as in the case of periarteritis nodosa, or lupus erythematosus.

One of our observations may serve as an illustration:

Patient B., 22 years of age, was brought to the neurological department of clinical hospital No. 4, on July 25, 1958. Did not complain about his health in the past. In March 1957, noticed for the first time that his vision was impaired, especially in the right eye, and it was gradually growing worse. In August, the diagnosis of secondary atrophy of the ophthalmic nerves was made. In October 1957, the auditory acuity was greatly weakened on both ears. In the two months that followed he developed a bilateral paralysis of the facial nerves. He acquired a nasal pronunciation and began to choke with his food. Hyperaemia of the left eye was observed in October; it was treated as ordinary conjunctivitis. The patient opened his mouth with difficulty and even that with the help of his hands.

Status praesens at the time of admission: Clear consciousness. Lymphatic glands not enlarged. No signs of pathological condition of the visceral organs.

The visual acuity of the right eye 0.08, of the left—0.1. Partial atrophy of the ophthalmic nerves in the eyeground of both eyes. Masseter muscles weakened.

Bilateral peripheral paralysis of facial nerves. Pronounced bilateral auditory impairment. Dysarthric speech. Chokes with food. Protrudes his tongue with difficulty, muscles of the tongue being atrophied. Atrophy of muscles of wrists and descreased power of these muscles. Tendon reflexes in the arms respond, rather sluggish.

X-ray examination of the cranium revealed no changes in bones. Blood count: Hb 78%, leukocytes 6,900, eosinophils 1%, band cells 1%, segmented cells 69%, lymphocytes 25%, monocytes 4%, erythrocyte sedimentation 5 mm per hour. Cerebrospinal fluid: pressure 120 mm, albumin 0.6‰, cytosis 2. Wassermann's reaction in blood and cerebrospinal fluid negative. Urine normal.

Bilateral lesions of the facial nerves, bilateral auditory disturbances and lesions of the caudal group of cranial nerves, in the absence of any indications of the involve-

ment of the conductive systems of the cerebral stem, leaves no doubt as to the localisation of the pathological process at the cranial base. The slow progress of the disorder which affects one cranial nerve after another, in the absence of pleocytosis in the cerebrospinal fluid, testifies against an inflammatory process in the membranes. A tumour at the base of the brain is excluded on the ground of the relatively benign course of the disease and the combination of lesions of the ophthalmic nerves with lesions of other cranial nerves, while all the oculomotor nerves remain completely intact. This "interruption" is incomprehensible in the case of a "creeping" tumour at the cranial base, but it is possible if the cranial nerves are compressed by diffuse granuloma, as it is observed in sarcoidosis.

An important diagnostic factor is the bilateral paralysis of the facial nerves. Jefferson, who collected a great amount of material on sarcoidosis of the nervous system, writes in this connection that simultaneous bilateral paralysis of the facial nerves is enough for supposing sarcoidosis, inasmuch as diplegia of the facial nerves is brought on most rarely by other causes. The severe restriction of movements of the mouth can be explained only by a mechanical cause, probably by the enlargement of the parotid glands which is often observed in sarcoidosis.

There is no difficulty in diagnosing sarcoidosis of the nervous system in the presence of symptoms of lesions in other organs, nodulated or dermatic plaques, enlargement of the salivary or lymphatic glands, lesions of the lungs, iridocyclitis. In the absence of these lesions the diagnosis becomes a very difficult problem the final solution of which can be achieved only on the basis of a histological examination of the material taken for a biopsy during the craniotomy, or laminectomy.

The disease develops slowly, with remissions and relapses. In some cases the involvement of different organs in the pathological process occurs in separate episodes. It is considered a benign disorder in view of the frequently

observed long spontaneous remissions. Involvement of the nervous system complicates the course of the disease and may lead to a fatal outcome.

The methods of treating sarcoidosis employed hitherto produced no effect. With the application of the adrenocorticotropic hormone and cortisone in medical practice reports have appeared about their effective use in sarcoidosis as well (Jefferson and others).

Chapter III

NERVOUS LESIONS ASSOCIATED WITH PULMONARY DISEASES

TUBERCULOSIS OF THE LUNGS

All forms of tuberculosis of the central nervous system (tuberculous meningitis, solitary tubercles of the cerebrum and spinal cord, lesions of the spinal cord in spondylitis tuberculosa) are secondary lesions, the primary focus being located in most cases in the lungs, or peribronchial lymphatic glands.

It is not the purpose of this book to describe various forms of tuberculosis of the central nervous system, and I shall therefore restrict myself to disorders accompanying tuberculosis of the lungs.

Vegetative Syndromes. Some of the symptoms observed in pulmonary tuberculosis are induced by direct action of the tubercular process upon the sympathetic nervous system and by viscerosensory and visceromotor reflexes. Mention should be made in the first place of anisocoria. According to some authors, it is observed in 50 per cent of the cases of pulmonary tuberculosis. Most frequently observed is the dilatation of the pupil on the affected side owing to irritation of the sympathetic fibers passing through the pleura of the lung apex. Anisocoria is observed more frequently in lesions of the supraapical pleura, rather than of the lung itself. Mydriasis is considered typical of the early stages of irritation of the pleura, and miosis—of the later scarring stage.

Irritation of the collateral trunk explains also other unilateral symptoms: hyperaemia of the cheek, or ear, their hidrosis and the feeling of fever. An artificial pneumothorax may lead to the abatement of these disorders, when the gas pressure is reduced in the pleural cavity. Cases with unilateral pigmentation of the face have been described.

Stimulation of vegetative nerves by tubercular foci induces a number of viscerosensory and visceromotor reflexes. An expression of the viscerosensory reflexes is represented by the hyperaesthetic zones (the Zakharin-Head zones). These zones for the lungs and bronchial tubes are the regions of innervation by the thoracic segments D_2-D_5 (D_7-D_8-D_9). Furthermore, hyperalgesia in the zone of innervation by the cervical segments C_3-C_4 is observed in some cases owing to the stimulation of the afferent fibers of the n. phrenicus. Stimulating impulses may spread centrifugally along the vagus, and, conveyed to the trigeminal nerve, cause hyperalgesia in the different regions through which the latter spreads.

According to Head, small fresh infiltrations are accompanied by distinct hyperaesthetic zones, but they are absent in far advanced processes in the lungs and lesions of the pleura. According to Head, they are absent also in pulmonary processes which are combined with the formation of cavities, because in these cases the sensory nerves are rapidly destroyed. Head's data have been confirmed by other investigators, but many authors have found Zakharin-Head zones in a very small number of cases. The appearance of these zones depends upon the patient's individuality and is observed chiefly in neurotic people. In some cases, hyperalgesia is concomitant with pain which is frequently mistaken for primary brachio-intercostal neuralgia, neuritis, myositis or for signs of intoxication. Pain caused by viscerosensory reflexes in tuberculosis of the lungs is of a dull, drawing rather than of a sharp character. It extends to the region innervated by the III cervical

and V thoracic segments of the spinal cord and are often accompanied, in addition to hyperalgesia, by hypersensitiveness to thermal irritations and sensitiveness to pressure.

Visceromotor reflexes are observed in the region of the same segments as the viscerosensory reflexes. Palpation reveals a spastic contraction of the sterno-cleido-mastoideus, scalenus, pectoralis, trapezius and levator anguli scapulae muscles on the side of the affected lung. Spastic contractions of separate muscular bundles are often observed. Singer observed attacks of muscular contractions in the left side of the chest in a patient with the focus of a fibrotic process in the left lung. Dilatation of the left pupil, pain in the left orbit and silvery hue of the left concha nasalis inferior were observed in the same patient.

Viscerotrophic reflexes are rare and they are expressed in moderate atrophy of the above-mentioned muscles. Hemiatrophy of the face with lesions in the lung apex and pleura are still rarer. In one such case the inferior cervico-sympathetic ganglion was involved in the scar. We have observed an isolated atrophy of the tongue on the side of the tubercular focus, and we consider this atrophy to be a trophic reflex the sensory impulses of which are directed along the vagus, and the efferent ones—along the sublingual nerve.

Reflectory symptoms may develop in pulmonary tuberculosis in consequence of the stimulation of the vagus. Stimuli are transmitted through the n. laringeus superior to the larynx and cause a compulsory tussiculation, weaken the vocal cords and draw them towards each other. That leads to various degrees of hoarseness and aphonia long before the tubercular process extends to the larynx. This visceromotor reflex in the vocal cords may occur also after pleurisy with subsequent adhesions and restriction of the lung excursion. We have observed a patient after pleurisy ending in the inosculation of the pleura in the costo-dia-

phragmal corner. The patient suffered from fits of irrepressible coughing after fast walking or several consecutive deep inhalations.

It is rather difficult to determine the pathogenesis of headaches in persons suffering from tuberculosis of the lungs. Some authors explain it by intoxication caused by absorption of products of disintegration of the tubercular foci and of exudates. In some cases headaches may possibly originate from a reflex mechanism. Stimulating impulses are directed controgenously along the vagus and transmitted to the trigeminal nerve causing pain in the zones innervated by it. In such cases, along with complaints of frequent and protracted headaches, moderate pain in the skull may be revealed by percussion, and pressure upon the eyeballs at the point of exit of the branches of the trigeminal nerve.

The state of the vegetative nervous system in pulmonary tuberculosis was widely discussed in connection with the concepts of vagotonia and sympathicotonia. It was held that tuberculosis was accompanied by hyper-excitability of the sympathetic nervous system. Clinical symptoms cited in support of that were: insusceptibility to adrenalin and high sensitiveness to pilocarpine, sweating, coughing, diarrhoea and pallor of the face. Some authors found in some patients a strong reaction to adrenalin in the early stage of pulmonary tuberculosis.

This means that they are sympathicotonics. And vice versa, vagotonia was considered characteristic of graver cases and of the later stage of tuberculosis. Patients with focal fibroid phthisis were classified among the sympathicotonics, and those with exudative forms—among the vagotonics. Later, most of the authors reached the conclusion that general lability and instability of the vegetative nervous system which is both hyper- and hypoamphotonic, as well as the excitability of the sympathetic and parasympathetic sections of the nervous system are observed in tuberculosis of the lungs.

Lesion of the vegetative nervous system conditioned by general tubercular intoxication accounts for a number of symptoms: hidrosis, vasomotor and pulse lability, etc.

Changes in ganglionic formations of the abdominal sympathetic nerve in the form of cellular disintegration, atrophy and inflammatory reaction have been found in grave forms of tuberculosis. Levin described pathological changes in the g. nodosum of the vagus. B. N. Mogilnitsky believes that the entire vagus is affected in pulmonary tuberculosis. In the sympathetic ganglia he found proliferations of connective tissue stroma, reduction in the number of cells, their atrophy and degeneration. Similar changes have been described by A. I. Abrikosov. Most striking pathological changes are found in regions adjoining the affected organs. On the basis of their pathological investigations V. V. Mikheyev and Y. M. Pavlyuchenko reached the conclusion that tuberculosis of the lungs causes diffuse changes in the vegetative centres, which suggests the existence of favourable conditions for the penetration of toxins into the central nervous system.

Tubercular Neuritis and Polyneuritis. In some cases tubercular lesion of the bronchial and mediastinal lymphatic glands and the pleura involves in the process the vagus and the phrenic nerve, as well as the spinal nerves. V. A. Ravich-Shcherbo and V. M. Goldfeld described in detail topical syndromes of lesions of specific nerves depending upon the localisation of pleurisy. They believe that neuralgias develop during an inflammation of the parietal pleura and that they are absent when the visceral pleura is involved. In an inflammatory process in the parietal pleura the authors distinguish four neurological syndromes the nature of which depends upon the location of the pleural lesion, its costal, supraapical, mediastinal and diaphragmal sections.

Lesion of the costal pleura brings on pain resembling intercostal neuralgia. It is a gnawing, drawing pain and

it is ordinarily localised in the back. Plexitis of the brachial plexus is characteristic of supraapical pleurisy. We have observed cases in which brachial plexitis with pain and paralysis developed rapidly following the appearance of pleurisy with exudation. It should be borne in mind that in the case of persisting plexitis without a clear etiology a thorough examination of the lungs should be made.

Lesion of the mediastinal section of the pleura leads to the development of visceral symptoms in the form of cardiac neurosis or disturbances of gastric secretion. Compression of the vagus nerves and the nn. accelerantes brings on attacks of acceleration and deceleration of the heart functioning, in some cases with anginose symptoms. Lesion of the recurrent nerve evokes spastic contractions of the glottis, hoarseness and aphonia. Compression of the phrenic nerve limits the mobility of the diaphragm on the respective side. Quite frequently the above-mentioned symptoms of lesions of the peripheral nerves are relieved or disappear with improvements in the pleuropulmonary condition.

In addition to these symptoms induced by the direct action of the pathological process, toxic neuritis and polyneuritis of the spinal nerves in pulmonary tuberculosis were described more than 50 years ago. Three forms of lesions of the peripheral nerves are distinguished in tuberculosis: atrophic, sensory and latent neuritis. More frequently encountered are neuritis, characterised by pain, paraesthesia, painfulness of the nervous trunks on compression and by sensorial disturbances. More rarely found are atrophic symmetrical paralysis with the disappearance of tendon reflexes, but with normal sensorium, or its mild disturbance.

As a result of histological examinations, Pitre and Veillare found in 40 per cent of persons suffering from tuberculosis more or less pronounced changes of the peripheral

nerves, "latent neuritis", which are not evident in the clinical picture.

Descriptions of neuritis associated with tuberculosis are given much rarer by modern authors. D. S. Futer did not observe them in many patients, S. D. Voznesensky found them in 28 out of 3,300 cases, and Levy-Valensi—in eight out of 2,000 patients.

Histological examinations reveal processes of disintegration of the myelin sheaths and fragmentation of the axis cylinders in the peripheral nerves. The nerve trunk is affected unevenly: along with bundles of degenerated fibers, entirely normal ones are also observed. There are descriptions of cases of segmental periaxial nephritis in which the process is limited to several segments and affects almost exclusively the myelin sheath. Swelling is observed in Schwann's sheath and endoneurium, but without typical inflammatory changes. Experiments on animals, conducted by Hammer revealed a state of tigrolysis in the motor cells of the spinal cord.

Neither tubercles, nor tubercular mycobacteria were found in the peripheral nerves during histological examinations. Rabbits with affected sections of the nerve were inoculated but that did not evoke any disease in them. According to Carrier only degenerative changes in the nerves were produced by inoculating rabbits with tuberculin over a period of 5-6 months.

The first authors to describe neuritis and polyneuritis in patients with tuberculosis noted that these patients were at the same time alcoholics. Only in isolated cases was it possible to exclude the alcoholic factor with certainty. M. S. Margulis believes that the combined action of other factors such as alcohol, chills, or infection can lead to the development of turbercular intoxication in the form of neuritis. An important part is most probably played also By Vitamin B_1 insufficiency owing to prolonged malnutrition (loss of appetite, vitamin insufficiency in the organism during the infection).

Consequently, lesions of peripheral nerves in pulmonary tuberculosis develop in most cases under the action of complex factors, the tubercular infection being one of the main links.

The prognosis of polyneuritis depends upon the state of the tubercular process. Recovery is more frequent when isolated nerves are affected.

Treatment is the same as that employed in other toxinfectious neuritis. Large doses of Vitamin B_1 are recommended. The treatment should be prescribed with due consideration for the gravity of the main tubercular process, which is often a contraindication to the use of active physiotherapeutic and balneotherapeutic treatment.

Serous Meningitis and Other Non-Specific Reactions. Serous meningitis, meningeal reaction of tubercular patients and abortive form of tuberculous meningitis are all synonymous. Their true nosological place and their relation to the tuberculous infection is as yet not clear enough.

In some patients suffering from tuberculosis headaches are combined with sensitiveness of the cranium to percussion, pain produced by pressure upon the eyeballs and increased patellar and Achilles tendon reflexes. Occipital rigidity and Kernig's sign are relatively rare. There are descriptions of cases in which a lumbar puncture revealed a high intracranial pressure as well as an increase in the number of lymphocytes and in the albumin content. In general, the clinical picture resembles to a certain degree the picture of tuberculous meningitis, but the patients either recover, or the diagnosis of tuberculous meningitis is not confirmed by post-mortem examinations. On the basis of his cases Quincke categorically denies the direct penetration of bacteria into the sheaths. Claude, on the contrary, believes that the tuberculous infection may also cause the abortive form of tuberculous meningitis. In one patient, who recovered after serous meningitis he observed subsequently a series of other localisations of the tubercular process (pleurisy, pericarditis, lymphadenitis of the cerv-

ical lymph nodes). In another patient, who died of tuberculous meningitis, an old cyst was found in the cerebral cortex.

Claude's arguments do not seem adequately convincing, inasmuch as in his cases histological examinations did not reveal the presence of either giant cells or of tubercular bacilli. Nor were any specific changes found at the post mortem in cases described by other authors.

Cases which ended in recovery are not adequately convincing. The certainty of this form will be proved only when old tubercular changes will have been found in the cerebral membranes of persons who died of other diseases. Clinical facts suggest the idea that this form is due to tuberculous intoxication.

Sharply pronounced meningeal symptoms are rarely observed in tuberculous pneumonia. The cerebrospinal fluid remains normal. This condition lasts for several days and in some cases turns into cerebellar ataxia which persists for several weeks or months. The disorder is caused by tuberculous intoxication. The prognosis in these cases is favourable, not only meningeal, but cerebral symptoms as well, disappearing in all the patients.

A. I. Geimanovich, R. M. Pinskaya and R. M. Korsunskaya described in cases of pulmonary tuberculosis the diencephalic and meningoradicular syndromes which they regard as nonspecific allergic reactions.

Embolism of the Cerebral Vessels During Artificial Pneumothorax. Descriptions have long ago been given of epileptic seizures during a pleural puncture, thoracocentesis and operations on the thorax. Forlanini, the first to introduce artificial pneumothorax in clinical practice, observed seizures of this kind and described them under the term of "pleural eclampsia". During the insufflation the patient suddenly becomes pale, loses consciousness, the skin becoming marble-like, arterial pressure falling; this is followed by the appearance of clonic convulsions which sometimes resemble the Jacksonian type of seizures. In

milder cases, transient mono- or hemiplegia with high tendon reflexes and pathological reflexes are observed instead of epileptic seizures; transient amaurosis is even rarer.

In most cases these symptoms disappear within a few hours, or days, very rarely leaving behind any residual symptoms.

Grave cases, however, may end in death. There are only few descriptions of cases with status epilepticus which ended in death. Seizures are observed in persons who do not suffer from epilepsy. On the other hand, the induction of a pneumothorax in patients affected with epilepsy does not provoke any convulsive seizures. The seizures may occur during the first insufflation as well as during subsequent ones. Forlanini considered them reflex seizures. The irritation produced in the pleura and lung by the needle, or gas, causes spastic contractions of the cerebral vessels which account for the convulsive seizure. Further studies of this question revealed that the seizures are evoked by gas embolism of the cerebral vessels. When the point of the needle introduced between the pleurae penetrates the lung tissue and the lumen of the pulmonary vein, the insufflated air penetrates through the heart into the cerebral vessels. The frequency of embolisms in the early period when the artificial pneumothorax was introduced as a method of treating tuberculosis of the lungs was explained by the absence of a valve in the first model of the apparatus used for artificial pneumothorax. Embolisms in connection with an artificial pneumothorax are exceptionally rare today.

CANCER OF THE LUNGS

Metastasis in the Central Nervous System. Along with the mammary gland, the bronchial tubes and the lungs are the most frequent sources of cancerous metastasis into the central nervous system. According to data published

in literature, 30-40 per cent of lung cancer give metastasis into the brain.

Out of 36 patients with cancer of the brain observed by us, four had gastric metastasis, two—from the urogenital sphere, one from the oesophagus, four—from the mammary gland, two—from the thyroid gland, and the remaining 23—from the bronchi and lungs. Our data reflect not only the frequency of metastasis of cancer of the lung into the brain, but also the frequent absence of symptoms in the place of its primary growth. Nervous symptoms stand out in the foreground; they obscure the pulmonary symptoms and often lead the specialists to diagnose the disorder as a primary tumour of the brain, cerebral apoplexy, meningo-encephalitis, etc. Solitary metastasis are much rarer than multiple ones. Solitary metastasis were found only in eight out of our mentioned 23 patients.

Focal symptoms of cerebral lesions correspond to the localisation of the metastasis. Noteworthy among the specific features of metastatic cancers are the frequent absence of symptoms of high intracranial pressure and very late appearance of engorged papillae. Focal symptoms may be faintly expressed, or without definite localisation, which is explained by the presence of several or multiple cancerous nodes in the brain. The clinical syndrome may in some cases develop intensely, without any signs of engorged papillae or other signs of high intracranial pressure.

Cancerous metastasis from the lungs are found much rarer in the membranes than in the cerebral substance. In that case, severe headaches are observed along with lesions of the craniocerebral nerves. Metastasis of this kind may be mistaken for syphilitic basal meningitis. Indications against syphilis in these cases are exceptionally severe headaches, the incessant progress of the disease, the intensity of the lesions of the cranial nerves and the absence of biological reactions to syphilis.

In some cases, multiple metastasis of cancer into the

pial membranes produce a clinical picture which resembles infectious meningitis. This is the so-called carcinomatous leptomeningitis which may be overlooked also in the post mortem, because it may be revealed only by microscopic examination. Clinically, in addition to meningeal symptoms, characteristic psychic changes are often observed; they are expressed in the alternation of psychomotor excitation with apathy and pronounced inertness.

At the pathological examination the metastatic nodes of the tumour are distinctly delimited and are extirpated with comparative ease. Degeneration and disintegration of tissue with the formation of a cyst may develop in the cancerous nodes during their growth. Acute oedema and numerous phagocytes are observed in the tissue around the cancerous metastasis.

The frequency of metastatic cancerous tumours of the brain with their primary localisation in the lungs suggests that an X-ray examination of the lungs must be made without fail when a tumour of the brain is found in persons over 40 years of age.

The development of the disorder may be acute, providing ground for the diagnosis of a cerebral stroke. Gradual improvement in clinical symptoms may be observed at times. Even at the autopsy it is not always easy to diagnose correctly, if a patch of softening is found in the region of the basin of a definite vessel. However, the cause of this softening is not an ordinary thrombosis of the blood vessels, but an embolism by cancerous cells. Moreover, the softening develops prior to the cancerous node. The disappearance of the perifocal oedema in the case of such a cancerous embolism may explain a certain remission of clinical symptoms.

Somatic symptoms are also important for the diagnosis: subfebrile temperature, shift to the left of the haemogram, high erythrocyte sedimentation, cachexia. E. K. Yevzerova notes in latent cancer of the lungs symptoms of intoxication such as headaches, persistent pain in the chest, pain

along the nerve trunks, hyporeflexia. All these symptoms are by far not constant.

It often happens that cancer of the upper lobe penetrates directly into the vertebrae; other bones of the skeleton are rarely affected. In some cases it may be difficult to detect a small node of primary cancer of the lung, but numerous metastasis may be observed into the bone system. The lower thoracic and lumbar vertebrae are affected most often.

In such cases there is usually a haematogenous metastasis into the spinal column with secondary compression of the spinal cord and its roots. In seventy patients suffering from cancerous metastasis into the spinal column Y. M. Polonskaya found 11 cases of primary localisations in the lungs. Cancer of the spinal column affects the body of the vertebrum and often involves several adjoining vertebrae. Compression of the spinal roots causes exceptionally severe pain. The dura mater is a stable barrier through which cancer of the spinal column penetrates very rarely into the spinal cord. Spinal symptoms are produced by compression and present a picture of compression myelitis. Three phases are distinguished in the development of cancer of the spinal column: neuralgic, spinal deformation and compression forms. It often happens that the rapid development of the disorder obliterates the boundaries between these phases. The clinical picture depends upon the level of the spinal lesion. The patient's age, severe pain and more rapid progress of the disease makes it possible in most cases to distinguish cancer of the spinal column from spondylitis. However, in cases when it is impossible to find the primary localisation of cancer, these symptoms may lead to an erroneous diagnosis, because in elderly people tuberculous spondylitis may acquire an acute form and lead rapidly to a lethal outcome. In such cases the question is decided by an X-ray examination.

Neuritis. Peripheral symptoms may be observed in cases of direct compression of the nerve roots and nerves by a

tumour. Girdle pain in the chest is indicative of the involvement of the intercostal nerve roots, and pain in the arm —of the involvement of the first thoracic root of the brachial plexus.

Compression of the recurrent nerve produces aphonia, attacks of dyspnoea and coughing. Paralysis of the recurrent nerve is usually indicative of the penetration of the cancerous tumour into the mediastinum. Compression of the vagus is expressed in acceleration or deceleration of the pulse and in fits of paroxysmal coughing. Compression of the phrenic nerve produces tormenting hiccuping and paralysis of the diaphragm.

Pancoast's Syndrome. Cancer of the lung located in the region of the apical lung fissure produces a specific combination of symptoms known as the Pancoast syndrome (1924). The symptoms observed are pain in the shoulder joint, Horner's syndrome and sometimes also atrophy of the minor muscles of the wrist. Owing to the involvement of the cervical sympathetic ganglion, sweating of the corresponding hand, and of the corresponding side of face and neck disappears. An *X*-ray examination reveals a destructive process at the base of the I-II cervical ribs. This syndrome is sometimes concomitant with oedema of the arm which is indicative of compression of the subclavian vein.

Polyneuritis. Cancer of the lung, just as malignant tumours localised elsewhere, is associated with typical polyneuritis which is believed to be caused by toxic factors, and, in particular, by intensified disintegration of albumin and by other toxic products of metabolism emanating from the tumour. In the opinion of V. V. Mikheyev, cancerous polyneuritis resemble the polyneuritis observed in alimentary distrophy and avitaminosis. The author connects their pathogenesis with cancerous cachexia. The development and gravity of polyneuritis may not correspond to the gravity of cachexia; therefore, when symptoms of polyneuritis appear in elderly people, the possibility of a

malignant tumour should be considered along with other causes.

In some cases the syndrome of simultaneous lesion of several peripheral nerves is caused by metastases, especially if the latter are located in the spinal column, or in the cranium. Enlarged lymphatic glands may cause compression of the cervical or lumbar plexus.

PNEUMONIA

Meningitis and Meningism. Most frequent and practically significant among the nervous lesions associated with croupous pneumonia is the meningeal syndrome. Meningeal symptoms are produced by lesions varying in genesis, clinical manifestations and course of development and are expressed in purulent meningitis, serous meningitis, or meningism. The first of these develops when the pneumococcus penetrates into the subarachnoic space. According to various authors, the frequency of pneumococcic meningitis in pneumonia fluctuates between 0.5 and 7 per cent. The cause of these fluctuations is the varying gravity of epidemics of pneumonia. Meningitis was observed most frequently in the years when pneumonia assumed especially grave forms. With the introduction of sulfanilamide preparations and antibiotics into medical practice there has been a sharp decline in meningeal complications during pneumonia.

Pneumococcic purulent meningitis appears at the height of pneumonia, and in some cases after the temperature drops. In this case, in addition to meningeal symptoms (occipital rigidity, Kernig's and Brudzinski's signs), the general condition of the patient takes a sharp turn for the worse. The patient grows pale. The temperature rises above 39°C., the spleen is enlarged and purpura often appears on the skin of the body. The clinical picture resembles that of epidemic meningitis and suggests the idea of severe pneumococcaemia. The cerebrospinal fluid is pu-

rulent with a large content of pneumococci which are easily detected in a smear. Epileptic seizures may sometimes appear at the very beginning of the disease. In the case of severe pneumonia in children meningeal symptoms may be obscured by the gravity of the pulmonary process and meningitis may then be discovered suddenly at the post-mortem examination. Ordinarily, vomiting, convulsions and a state of stupor signalise the appearance of meningitis in children.

As in the case of epidemic meningitis, the purulent exudate is located mainly at the cerebral arch. The cerebral ventricles are filled with a turbid liquid. Lesion of the meninges alone is rarely found at post-mortem examinations. Pleurisy, pericarditis, and endocarditis point to a general infection, meningitis representing one of its localisations. The course of the disease is brief and prior to the introduction of sulfanilamide preparations and antibiotics the vast majority of cases ended in a lethal outcome within 5-10 days. However even when sulfanilamides are used, the mortality rate, according to our information, remains above 80 per cent. Considerably better results are produced by treatment with penicillin and broad-spectrum antibiotics.

Serous Meningitis. Meningeal symptoms appear earlier than in purulent pneumococcic meningitis, ordinarily on the second day of the disease. Kernig's and Brudzinski's signs may be as pronounced as in purulent meningitis, but the general severe symptoms accompanying purulent meningitis are absent. Unlike the latter, the cerebrospinal fluid, dripping under great pressure, is transparent and contains lymphocytes and not neutrophils. Pneumococci are not found in it.

The relation of serous meningitis to the pneumococcic infection remains unclear to this day. The absence of neutrophils and the sterility of the cerebrospinal fluid leads us to assume that what we have here is a case of aseptic toxic meningitis. Descriptions of cases in which serous

meningitis subsequently transformed into a purulent one has prompted some authors to consider it an abortive form of pneumococcic meningitis. At any rate, for practical reasons, it is important to single out this form, because, unlike purulent meningitis, its prognosis is almost always favourable. Only in isolated cases, of which descriptions are available, were epileptic seizures, or development of hydrocephalus, observed.

Meningism is observed most frequently in children and it develops at the very beginning of the disease, quite often prior to the appearance of distinct symptoms of pneumonia. Ordinarily, vague meningeal symptoms, headaches, and sometimes vomiting, are observed in this case. In some cases there is a distinct picture of meningitis with dimmed consciousness and severe occipital rigidity. The cerebrospinal fluid in meningism is normal. Nor does a thorough histological examination reveal any changes in the meninges. Meningism is apparently caused by a sharp rise in intracranial pressure. Hypotonia induced in an animal by intravenal injection of aqua destillata results in a rapid increase in intracranial pressure. It may be assumed that a similar increase in intracranial pressure takes place at the beginning of pneumonia. The above-mentioned considerations are confirmed in practice by the successful treatment of the disease with lumbar puncture and intravenal injections of hypertonic solutions. The prognosis in meningism is unquestionably favourable. Although meningeal symptoms are less pronounced in meningism and serous meningitis, the decisive diagnostic factors are a lumbar puncture and examination of the cerebrospinal fluid.

Focal Lesions of the Brain. Comparatively rare cases of pneumonia are complicated by hemiparesis or hemiplegia. The causes of the latter in pneumonia are apparently variable. In the cases of pneumococcic sepsis and endocarditis hemiplegia, is caused by embolism of the cerebral vessels. There are cases in which lesions of the cardiac valves can-

not be detected by a physical examination. Sudden development of hemiplegia leads us always to assume the existence of endocarditis. In children affected with pneumonia hemiplegia may appear acutely and subside completely within a few days. This type of hemiplegia is probably due to oedema of the brain. In aged people hemiplegia may develop at the height of the disease. The patient suddenly develops a picture of a cerebrovascular accident with coma, paralysis of the extremities, and in some cases compulsory turns of the head and eyes. The patients usually die within a few days or even hours. These cerebrovascular accidents are caused by a decline of heart functioning which leads to ischemic softening.

Complications of the central nervous system are observed not only in croupous pneumonia, but also in inflammations of the lungs of varying etiology. Headaches, vomiting, giddiness and drowziness appear at the height of the disease, or in the stage when the temperature has already dropped. Severe cases are associated with convulsive seizures, delirium, comatose states and hemiplegia. These phenomena may appear also several days or even weeks after the temperature has dropped and the patient has begun to recover from pneumonia. The appearance of cerebral symptoms does not depend upon the gravity of pneumonia. The cerebral symptoms prolong the disease. In many cases recovery is accompanied by residual symptoms.

These nervous complications are explained by different causes: intoxication, spontaneous penetration of the pathogenic factor of pneumonia into the brain, anoxaemia, allergic reaction. Noran and Baker described a histopathological picture in the brain in 10 cases of pneumonia with cerebral complications. Notwithstanding the difference in the etiological factors of pneumonia, they found an analogous picture expressed in petechial haemorrhages and in the formation of numerous thrombi in the small vessels. In graver cases, thrombi composed of fibrin were found

in the major vessels. Many minor vessels are surrounded by an erythrocytic ring or by a small perivascular zone of demyelinisation.

The identity of histopathological changes in pneumonia of varying etiology has led authors to the conclusion that these changes are caused by products of the disintegrated pulmonary tissue rather than by infection. Scheinker also considers, on the basis of 13 cases observed by him that changes in the brain are caused by disturbances of cerebral blood circulation in consequence of vasothrombosis, rather than by an inflammatory process. After injecting 31 rabbits with lung extracts, Noran and Baker found in the rabbits' brain changes similar to those observed in the human brain during pneumonia.

Polyneuritis. Polyneuritis is very rare in pneumonia. It develops at the time when the temperature drops or during reconvalescence, a few days or weeks after the crisis. It develops gradually, and only in rare cases may be acute. The disorder begins with unpleasant sensations and paraesthesia in the lower extremities, that is followed by weakness of the lower extremities and in much rarer cases—in the upper extremities; sensorial disturbances are observed in some cases in distal parts of the extremities, tendon reflexes decline or disappear in the lower extremities. The prognosis of this type of polyneuritis is favourable: as a rule it ends with gradual complete recovery. The pathogenesis of the disorder remains unclear.

PULMONARY ABSCESS

In cases of abscesses of the lungs, pulmonary gangrene, empyema and the bronchiectatic disease, the abscess of the brain originates as the result of septic embolism. According to R. A. Shakhnovich, 8.5 per cent of 72 abscesses of the brain were metastatic abscesses from the lungs. Schorstein found bronchiectasis in 28 out of 60 patients

with metastatic cerebral abscesses from the lungs. Metastatic abscesses from the lungs are often multiple abscesses.

Due to modern methods of treatment, metastatic cerebral absceses from the lungs are observed much rarer today, but it is still very difficult to discern them. Before the introduction of antibiotics into medical practice, the clinical picture of an abscess of the brain developed with sweeping speed and was marked by rapid disturbances of consciousness, the development of paralysis. Death occurred within 7-12 days. At present, following prolonged treatment with antibiotics, the first symptoms of an abscess are expressed in moderate headaches and in some cases in general or Jacksonian epileptic seizures and mild pyramid symptoms. Initial signs of engorged papillae appear only 2.3 weeks later. The general condition of the patient remains quite satisfactory and the disease is often mistaken for a disorder of cerebral circulation or cerebral thrombophlebitis.

PULMONARY EMPHYSEMA

Nervous symptoms in emphysema of the lungs may appear in the far advanced stage of the disease when signs of cardiopulmonary insufficiency become highly pronounced. In the case of a so-called pulmonary heart, the overexertion of the right ventricle of the heart leads to its rapidly decompensation, to disturbances of the oxygen and carbon dioxide exchanges with cyanosis and reactive polyglobulia which account for cerebral disturbances. In similar cases the patients become phlegmatic, apathetic, with disturbances of consciousness, and in rare cases—with epileptic seizures, delirium and coma. Focal symptoms, such as diplopia, disturbances of speech, vision, etc., are observed rarely.

Descriptions have been published in the last ten years of cases of emphysema of the lungs with the high intra-

cranial pressure syndrome and engorged papillae (Fuller). M. I. Kholodenko found in some patients with dextral insufficiency in the case of a pulmonary heart a "venous encephalopathy" in which he observed a pseudotumour syndrome, states of unconsciousness connected with fits of coughing and moderately expressed diffuse organic focal symptoms. Transient hemiplegia caused by venous stasis was observed in other patients. The fact that no nervous symptoms were observed in other patients is explained by M. I. Kholodenko by the adaptation of the brain to the slowly rising venous pressure.

The intracranial tension syndrome in emphysema of the lungs is expressed in progressing headaches combined in some cases with vomiting, drowziness, a dazed and confusional state. The headaches become more intense at night and in the early hours of the morning. Some of the patients are possessed by hallucinations and fear when they are in a horizontal position, which regress when the patient is set up. As a rule, focal symptoms are not observed. Jerks or trembling of the extremities are rare. Engorged papillae and, in rarer cases, blood effusions into the retina, are found in the eyeground. Pressure of the cerebrospinal fluid is sharply increased.

Highly pronounced signs of pulmonary emphysema, dispnoea and pulmonary heart are observed in such patients. Their venous pressure is usually very high. When cardiopulmonary symptoms abate, the signs of high intracranial pressure may become greatly attenuated and the engorged papillae disappear.

The syndrome of high intracranial pressure in emphysema of the lungs described above is caused by dilatation of the cerebral vessels brought on by hypoxia and hypercapnia. It has been proved that an excess of carbon dioxide in the blood raises the pressure in the cerebrospinal fluid. Respiratory acidosis and high intracranial pressure result in cerebral oedema. That creates a vicious circle: cerebral oedema in its turn decelerates the cerebral

blood circulation, producing hypoxia, increased transudation which cause a still higher intracranial pressure.

Sympson found in autopsies symptoms of cerebral oedema and pronounced stasis in the cerebral vessels. In four cases he found a dislocation of the cerebellar amygdala into the occipital foramen (cerebellar cone) caused by high intracranial pressure.

Only in a small number of cases is reactive erythraemia apparently the cause of high intracranial pressure and of the appearance of engorged papillae. Austen and Carmichael found erythraemia only in four out of 11 patients suffering from high intracranial pressure observed by them in emphysema of the lungs.

Chapter IV

NERVOUS LESIONS ASSOCIATED WITH DISEASES OF THE DIGESTIVE SYSTEM

THE ULCEROUS DISEASE

The role of the central nervous system in the origin of the ulcerous disease has been well established by N. N. Burdenko and B. M. Mogilnitsky, K. M. Bykov and I. T. Kurtsin, O. L. Gordon and other Russian authors. On the other hand, pathological afferent impulses emanating from the stomach affect the central nervous system. These impulses may serve to explain such vegetative symptoms as disorders of metabolism, temperature and sleep, and tachycardia observed in the ulcerous disease. Vonderahe found in 14 cases of ulcer (seven cases of duodenal ulcer, six cases of gastric ulcer, and one case of gastroduodenal ulcer) hyperaemia of the cerebral vessels and in some cases—extravasations in the dorsal nucleus of the n. vagus, in the substantia grisea of the III ventricle and in the n. reuniens of the hypothalamus.

We have observed similar changes in the case of gastric tetany following gastroenterostomy. In this case, an examination of the brain revealed only an excessive repletion of the cerebral blood vessels and membranes. A microscopic examination of the cerebral cortex revealed no changes in the white substance of the hemispheres and subcortical ganglia. In the diencephalon punctuate haem-

orrhages were found in the region of the anterior hypothalamus and paraventricular nucleus. The nerve cells in the area of the haemorrhages were destroyed, some of the cells were inflated, representing a picture of diffuse chromatolysis. Numerous punctuate haemorrhages were found in the covering of the medulla oblongata. The haemorrhages were located chiefly at the bottom of the IV ventricle, in the region of the dorsal nucleus of the n. vagus and at the inner edge of the roots of the eighth pair of cranial nerves. Vonderahe believes that these haemorrhages were caused by afferent impulses emanating from a peptic ulcer. Intense and constant irritating impulses passing along the visceral and sensorial pathways towards the hypothalamus and dorsal nucleus of the n. vagus, cause in these regions dilatation of the blood vessels, stasis and punctuate haemorrhages. Some experimental data may be cited in support of this viewpoint. Stimulation of the n. vagus results in dilatation of the cerebral vessels.

Consequently, irritations emanating from an ulcer may cause vasomotor disturbances in the region of the hypothalamus and nucleus of the tenth pair of cranial nerves, with subsequent blood effusions. These vasomotor disturbances may explain to some extent certain clinical symptoms. A frequent, easily excitable pulse and hidrosis are ascribed to lesions of the dorsal nucleus of the n.vagus; high excitability, emotional disturbances, disorders of metabolism and temperature are connected with the action of stimulating impulses upon the diencephalon. In reality, the pathogenesis of neurotic influences is much more complicated in this case. As the work of K. M. Bykov and his collaborators has shown, one of the major causes of neurosis lies in disturbances of cortical functions under the action of interoceptive reflexes.

POLYNEURITIS ASSOCIATED WITH INTESTINAL DISEASES

Concepts of the role of intestinal autointoxication in the origin of various diseases are among the most ancient on record in medical history. In the 19th century it was still believed that intestinal autointoxication was responsible for many diseases, as, for example, psychic disturbances, Bright's disease, epilepsy, arterial hypertension.

Modern medicine denies the role of autointoxication in the origin of these diseases. Alvarez even believes that the unpleasant sensations felt by some patients as the result of constipation are due not to autointoxication, but to the distension of the rectum and pressure upon its nerve endings.

Nevertheless, some neuropathologists believed that polyneuritis of indefinite etiology following gastrointestinal symptoms may be caused by intestinal autointoxication. It was held that fermentation processes in the intestines lead to ptomaine intoxication which induces toxic polyneuritis. Even at the end of the 19th century, the clinical syndrome marked by subfebrile temperature, pain in the region of the sigmoid flexure, constipation, diarrhoea and pain along the peripheral nerves, was still described as enterotoxic polyneuritis. M. N. Polyakov and V. K. Khoroshko described a case of polyneuritis which developed after constipation and pain along the intestines. Polyneuritis was discovered at the post-mortem examination. Toxins of the culture of the B. coli obtained from the patient's feces induced in guinea pigs an identical clinical and pathological picture.

Klippel, Mathiex and Weil emphasise that a gastric ulcer may be accompanied by a typical picture of polyneuritis which the authors explain by intoxication resulting from the destruction of gastric tissue. P. M. Saradzhishvili has

distinguished a group of polyradiculoneuritis associated with achylia.

Recent investigations suggest the idea that the basic role in the origin of polyneuritis in disorders of the gastrointestinal tract is played by factors connected with nutrition deficiency. In such cases, achylia, an irrational diet in combination with the lack of appetite, may easily cause the development of avitaminotic polyneuritis. Neurasthenic and vegetative syndromes described as signs of intoxication should be considered in the light of avitaminosis and hypoavitaminosis, and of K. M. Bykov's theory about interoceptors. They include a state of depression, high fatigability in which a slight strain is attended with pain of indefinite localisation, giddiness and prostration. The connection of their cause with diseases of the digestive organs is proved by the fact that all these symptoms disappear rapidly after the successful treatment of disorders of the gastrointestinal tract.

One of the most frequent symptoms of gastrointestinal disorders is vomiting. The general practitioner should remember that vomiting is a complex reflex action produced by many nerve pathways and the vomiting centre of the cerebral stem. Nerve pathways correlate the gastrointestinal activity with contractions of the diaphragm and of the muscles of the abdominal wall. The vomiting mechanism may be put into action by irritating various parts of the organism: the gastrointestinal tract, the uterus, kidneys, heart, inner ear and brain. The disregarding of these facts may lead to dangerous consequences, for in cases when vomiting is conditioned by meningitis, a haemorrhage into the brain and its membranes, or other cerebral disorders, its acute appearance might prompt doctors to recommend lavation of the stomach which is dangerous for the patients. Therefore in such cases it is necessary to exclude a primary cerebral disorder.

WERNICKE'S HAEMORRHAGIC POLIOENCEPHALITIS

Severe gastrointestinal disorders are complicated in some cases by cerebral lesions known as Wernicke's disease (acute haemorrhagic polioencephalitis). In most cases this lesion is connected with chronic alcoholism; and yet, in one of the three cases first described by Wernicke (1881), this disorder was not connected with alcoholism, but with pyloric stenosis developed after the patient had tried to commit suicide by swallowing sulphuric acid. Subsequently, Wernicke's haemorrhagic polioencephalitis was described in cases of cancer of the oesophagus, and stomach, gastric resection, gastroenteroanastomosis, chronic gastritis, cholecystostomy and pernicious hyperemesis gravidarum. Modern authors believe that even in the case of alcoholism Wernicke's haemorrhagic polioencephalitis is caused not by intoxication, that it is a "deficiency disorder" produced by the insufficiency of Vitamin B_1 in combination with gastroduodenitis, lesions of the liver and of the pancreas which accompany chronic alcoholism.

The clinical picture of the disease often begins with a moderately expressed delirious state which may last for several weeks. It is followed later by drowziness, and rarer —by stupor. Acute anorexia, vomiting and nausea appear. An objective examination reveals oculomotor disturbances, nystagmus, ataxia and, in some cases, muscular rigidity. Choreiform jerks of the extremities are observed in rarer cases. Tachycardia, disturbances of respiration and heart failure develop shortly thereafter. In some cases the picture described above is combined with Korsakoff's syndrome and polyneuritis. The disease progresses rapidly and in the absence of treatment ends fatally within 10-20 days.

Ordinarily, no changes in the brain are revealed by a macroscopic examination. Histopathological examinations reveal bilateral, and often symmetrical, foci of degeneration in the grey substance, around the III ventricle and the

sylviduct, as well as in the corpora mamillaria. In addition to the upper part of the cerebral stem, its lower part is also affected: the bottom of the IV ventricle and the inferior olive. Vasoproliferation, resembling granulation tissue, is evident in the affected regions. The walls of the blood vessels are thickened, and so is their endothelium, the vessels are distended, pletoric, and surrounded by small diapedetic haemorrhages. Considerable proliferation of neuroglia is also observed, while the nerve cells are in a state of acute degeneration. No signs of inflammation are found in the brain.

Consequently, the name proposed by Wernicke for this disorder, polioencephalitis haemorrhagica superior, does not reflect the real nature of the disorder, which is not a haemorrhagic encephalitis; it affects not only the grey cerebral substance and its localisation is not limited to the upper part of the stem. It would therefore be more correctly called Wernicke's encephalopathy.

Contemporary authors believe that Wernicke's encephalopathy is caused by Vitamin B_1 deficiency. In addition to avitaminosis, toxic factors and destruction of the haematoencephalic barrier are of great significance. There are reports on the successful treatment of the disease with parenteral administration of large doses of Vitamin B_1.

It should be emphasised that Wernicke's encephalopathy is observed very rarely today. K. Neubuerger reported at the London Congress of Neuropathologists, in 1955, that Wernicke's encephalopathy is rarely observed today even in patients suffering from chronic alcoholism, which, in his opinion, is explained by improved nutrition and popularisation of vitamins.

Chapter V

NERVOUS LESIONS IN DISEASES OF THE LIVER

The concepts of the connection between cerebral activity and functions of the liver was widely current among ancient doctors. Hippocrates believed that "depending upon the connection of a cerebral disorder with disturbances of salivation, or bile secretion, psychic patients are either melancholy, depressed and obsessed by fear, or, on the contrary, violent and destructive". It has long been noted that persons suffering from diseases of the liver are bitter, irritable and depressed. Esquirol directed attention to lesions of the liver in depressive states. Special emphasis was made in the 19th century on the role played by disturbances of hepatic functions in the origin of some types of psychosis, and there was distinguished a particular form of a psychotic state—folie hepatique.

M. I. Astvatsaturov emphasises the frequent outbreaks of anger in persons suffering from diseases of the liver.

"An inclination to irritability," he writes, "is observed precisely in the earlier stages of catarrhal jaundice, when neither pain, nor signs of jaundice, nor general symptoms of hepatic disorder are in evidence. The specific mood of patients suffering from catarrhal jaundice described here cannot be considered a consequence of painful sensations, or biliary intoxication, but it should belong in the sphere of a direct visceropsychic reversal."

M. I. Astvatsaturov points out that the emotion of anger is connected with the appearance of considerable amounts of adrenalin in the blood, with the high tonicity of the sympathetic nerve and intensified conversion of glycogen into glucose by the liver. Stimulation of the sympathetic nervous system in diseases of the liver is the initial factor which brings into action the entire complex of phenomena comprising the correlation between the emotion of anger and the function of the liver. The "viscero-emotive reversal" (the liver—emotion of anger) may be regarded as the reverse consecutiveness of the philogenetically established cycle of phenomena, "emotion of anger —stimulation of the sympathetic system of the liver".

According to a hypothesis advanced at the end of the 19th century, biliary intoxication was the cause of nervous disturbances in diseases of the liver. Administrating bile and studying the symptoms of intoxication induced thereby in animals, scientists tried to place the theory of cholaemia upon an experimental basis. They succeeded in proving experimentally the toxic action exerted upon the nervous system by bile obtained from the human organism by duodenal sounding. A subcutaneous injection of bile produced in mice, rabbits, pigeons and cats a state of stupor, or pathological sleep with muscular relaxation. Hiccuping, bradypnoea and sudden death were also observed. Catalepsy was produced in pigeons by repeated injections. Administration of large doses of bile resulted in paralysis with general tremor, disturbances of respiration and death of the animal. Rabbits and cats possess a higher resistance to biliary intoxication, but paralysis of the hind extremities was observed in them as well. In subsequent experiments similar symptoms were produced by administering bile salts, but not once was it possible to produce a stupor and catalepsy, as is the case when whole bile was administered. This fact suggested the idea that the last two symptoms are called forth by a toxic substance which bile salts do not contain. Some authors were emphatically

opposed to the theory of cholaemia. They insisted that an increase in the amount of bile in the blood was not of decisive importance. In their opinion, the etiological factor of intoxication lies in the accumulation of intermediate products of protein and carbohydrate metabolism.

Already at the end of the last century I. P. Pavlov demonstrated that a ligature of the bile duct and formation of an Eck fistula induces a state of excitation in a dog followed by apathy, drowsiness, convulsions and, lastly, death in a state of coma a few weeks after the operation. Histological examinations of the brain of the animals which thus perished revealed oedema of the brain, neuronophagia and proliferation of glial elements. The changes were of a diffuse nature, but they were more pronounced in the subcortical ganglia. Baló and Korpassy reproduced the experiment in 1932. In six out of eight dogs with Eck's fistula, they found symptoms of encephalitis which were intensified under the action of a mixed diet. Histological examinations revealed a picture of nonpurulent encephalitis localised mainly in the subcortical ganglia (perivascular infiltration by lymphocytic cells, accumulations of adventitial cells, micro- and oligodendroglial proliferation with their degenerative changes). Oedema of the cerebral membranes, capillary haemorrhages in the cerebral cortex and hyperplasia of the ventricular ependyma were found at the same time.

Different explanations are given for the above-mentioned phenomena. Cerebral lesions may be caused by toxic substances from the intestines which are not detained by the impaired liver, or by substances formed directly in the liver. Especially noteworthy is the role of the animal's diet. A dog fed on milk alone remains healthy at times, while the inclusion of meat in his ration causes a convulsive seizure. A similar picture is observed in guanidine intoxication. An injection of guanidine causes changes in the animal's nerve cells and neuroglia, especially in the subcortical ganglia, in Luy's body and in the substantia nigra.

The mentioned experiments are indicative of the toxic significance of guanidine, but the chemical factor responsible for the intoxication is still unknown. Referring to the picture of meningitis in the terminal stages of hepatic insufficiency, some authors point to the significance of polypeptide accumulation in the blood and in the cerebrospinal fluid.

After the ligature of the bile duct and of the pancreatic duct (a ligature of the pancreatic duct leads to the fatty degeneration of the liver), Crandall and Weil found in the blood serum a toxic substance which causes destruction of the brain in mice. This substance penetrates into the brain through the vascular plexus and the walls of the cerebral vessels. A histological examination revealed a spongy necrosis of the ventricular walls and cerebral cortex, diffuse lesions of the cells and glial proliferation. Mesenchymal elements are not involved into the pathological process. Similar results were obtained by reproducing the experiment on three dogs. The authors compare the results of their experiment with the histopathological picture in Wilson's disease and find that they have the following features in common: spongy necrosis of the nervous tissue, active glial proliferation with the formation of big Alzheimer's cells, diffuse degeneration of the cells with predominant localisation in the deep regions of the cortex and corpus striatum, and the absence of an active mesenchymal reaction.

The above-mentioned experimental investigations prove that hepatic insufficiency induces a specific toxic encephalitis, and the serum of an animal with impaired liver is toxic for the nervous system of another animal.

Diseases of the liver are often complicated by nervous lesions. Botkin's disease (icterus febribis) may sometimes be complicated by polyneuritis.

Cancer of the liver may also cause polyneuritis owing to the action of toxic substances conditioned by the malignant growth. Still more often cancer metastasises into the

spinal column producing a picture of compression myelitis.

Syphilis of the liver is often concomitant with syphilis of the nervous system. Echinococcosis of the liver may be combined with echinococcosis of the brain. Gallstones may be associated with paraesthesia in the right shoulder. Most significant and most interesting, however, is cirrhosis of the liver combined with lenticular degeneration and polyneuritis.

HEPATOLENTICULAR DEGENERATION

Most vivid proof of the connection of hepatic diseases with lesions of the nervous system is afforded by hepatolenticular degeneration, in which characteristic changes in the brain are almost always associated with cirrhosis of the liver. The disorder was first described by Wilson in 1912, as a disease observed in several members of one family. The disease begins at the age of 10-20, and progresses steadily with the development of cachexia and often with exacerbations. Wilson distinguished two forms of the disease: acute and chronic. Characteristic symptoms of the acute form is fever, rapid progress of the disease and a relatively fast lethal outcome (within 2-12 months). The chronic form may last for many years.

Initial symptoms of the disease are: dysarthria, moderate tremor of the hands and deceleration of volitional movements. In the more pronounced phase of the disease the face acquires a masklike expression with a fixed smile and open mouth, often with uncontrolled salivation; extrapyramid rigidity of the muscles observed in these cases resembles the muscular rigidity in parkinsonism.

The second characteristic feature of the disease is tremor which tends to increase with volitional movement and under the influence of emotions. This tremor is especially pronounced in the fingers and wrists. It is caused by rhythmic contractions of the antagonistic muscles with

a frequency ranging from 4 to 8 per second. The tremor usually appears simultaneously with muscular rigidity, but in some cases it appears many months and even years before the rigidity. In some cases tremor appears together with choreiform or athetoid movements.

As already mentioned here, one of the first signs of the disease is dysarthria which may result in complete anarthria. This is often combined with difficulty in swallowing. Polydipsia, haemorrhagic diathesis, epileptic seizures, diplopia and osteoporosis are observed in rare cases. Psychic disturbances are frequent, but they do not represent anything characteristic of the disease. Highly pronounced dementia may develop in the later stages.

As far back as 1883, Westphal described under the name of pseudosclerosis a similiar disorder, a characteristic symptom of which, in addition to the extrapyramid syndrome, was a greenish-brown ring in the cornea, around the pupil (Kayser-Fleischer ring). It is now considered that Wilson's disease and Westphal's pseudosclerosis are different forms of the same disorder.

Nervous symptoms are combined with cirrhosis of the liver. Most scientists are of the opinion that it is an ordinary sclerosis of the liver. Some believe that cirrhosis has as a characteristic feature an extremely abundant vascularisation of the hepatic parenchyma; precisely that accounts for the absence of signs of hypertension in the portal system. Sclerosis observed in the liver is sometimes also found in the spleen and pancreas, mainly in the Langerhans' islands.

In vast majority of cases the lesion of the liver is not expressed in the clinical picture. Nor is anything characteristic revealed in most cases by functional liver tests. In rare cases signs of functional liver disturbances are found in the form of easily provoked hyperglycaemia and glycosuria, and in changes in the ratio of blood albumins. A case of transient jaundice which originated 4-5 years prior to the appearance of the first nervous symp-

toms has been described. Signs of acute hepatitis and cirrhosis were observed also in other members of the family of the patient suffering from hepatolenticular degeneration. While in Wilson's disease the spleen is ordinarily very moderately enlarged, splenomegaly is observed in cases of Westphal's pseudosclerosis.

In 1948, N. V. Konovalov* published a monograph under the title *Hepatolenticular Degeneration* which contains a comprehensive analysis of questions relating to the clinic, etiology, pathogenesis and pathomorphology of the disease. On the basis of his own investigations and data obtained from literature N. V. Konovalov distinguishes the following forms of hepatolenticular degeneration:

1. Abdominal form, in which severe changes in the liver appear early and the patient may die before the appearance of pronounced nervous symptoms.

2. Arythmo-hyperkinetic form, in which early changes in the liver are also observed, while in the clinical picture of nervous lesions symptoms of hyperkinesis prevail over rigidity. Difficulties in swallowing and disturbances of speech appear rapidly.

3. Tremulous-rigid form. Signs of nervous lesions develop late. Tremor and rigidity appear simultaneously. Remissions are observed in the course of the disease. Clinical symptoms of hepatic lesions are very moderate.

4. Tremulous form. Distinguished by pronounced tremor and the absence of rigidity. The patient develops scanned speech. Mental deficiency is often observed. The disorder progresses slowly and in the terminal phase it may result in grave cachexia.

The Kayser-Fleischer ring is found only in some of the patients. It is expressed in the accumulation of greenish-yellow, or greenish-brown pigment in the Descemet's mem-

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* In 1960, N. V. Konovalov published his monograph *Hepatocerebral Distrophy*, for which he was awarded a Lenin Prize in 1961.

brane of the cornea. Gerlach and Rohrschneider found that this pigment consists mainly of copper. That was subsequently confirmed by Brand, Takáts and others.

Post-mortem examinations reveal a bilateral, symmetrical lesion of the lenticular nuclei and, to a lesser degree,

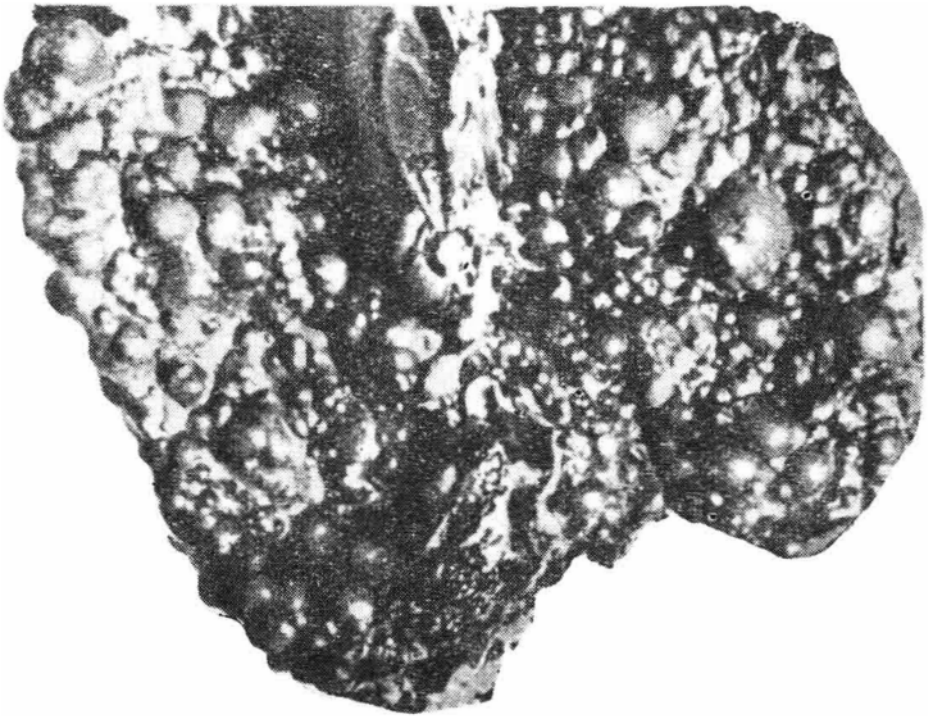

Fig. 27. Cirrhosis of the liver in hepatolenticular degeneration

of the globus pallidum. They seem smaller in size and in slices they have the appearance of a sponge with cavities and cysts. Microscopic examinations reveal atrophy and degeneration of nerve cells of the lenticular nucleus. Glial changes are expressed in intense formation of granular globes and proliferation of microglia which is rapidly undergoing regressive changes. Replacement of the disintegrated nerve cells by glial fibrosis is poor and inadequate. A characteristic feature is the appearance of Alzheimer's giant glia cells. (Fig. 27.)

It is not a systemic process, focal rarefactions and softenings being found in the caudate nucleus, the dentate nucleus of the cerebellum and the cerebral cortex. The process may extend to the neighbouring regions of the internal and external capsule. (Fig. 28.)

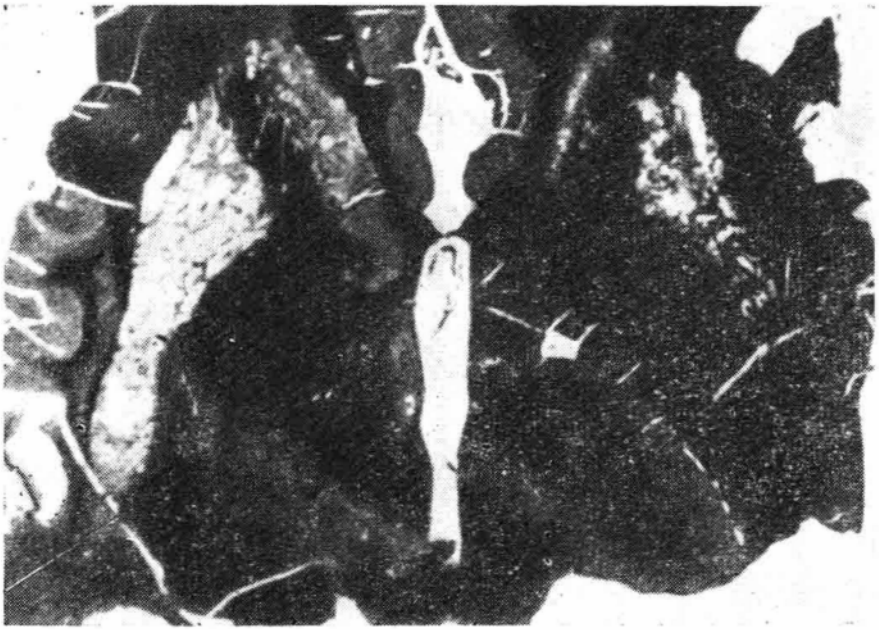

Fig. 28. Degeneration of the n. caudatus and putamen in hepatolenticular degeneration

The basic role in the pathogenesis of focal softenings is played, in N. V. Konovalov's opinion, by circulatory disturbances in the minor cerebral vessels caused by atonia of their walls. These circulatory disorders condition anoxia and destruction of nerve cells.

A constant symptom of the disease is cirrhosis of the liver. The liver is small, dense, with a lighter colouring than normally. Its surface is covered with numerous characteristic nodules. A microscopic examination reveals, along with small foci of necrosis, patches of degeneration and regeneration of the hepatic tissue. Connective-tissue par-

titions separate these sections from normal tissue. The liver contains a great number of vacuoles and marked proliferation of the bile ducts is observed.

Cirrhosis of the liver is sometimes observed in various striopallidary disturbances. It has been observed repeatedly in cases of chronic post-encephalitic syndromes. Bolsi described more than 20 cases of hepatic lesions in parkinsonism and torsion spasms. Van Bogaert observed a case of extrapyramid affection with akinesia, amimia, greenish-brown ring around the iris and pigmentation of the skin. The subsequent diagnosis was trypanosomiasis. A histological examination revealed the presence of the same pigment which reacts to iron in the liver, spleen and central nervous system. The disorder developed through the following stages: trypanosomiasis induced cirrhosis, which in its turn conditioned lesions of the nervous system. There are descriptions of cases of Huntington's chorea in which hypertrophic cirrhosis of the liver was found along with changes in the putamen. Combinations of focal disintegration in the corpus striatum with cirrhosis of the liver of the Laennec type are sometimes observed in persons affected by the senile extrapyramid syndrome.

There are three different theories which explain the connection between lesions of subcortical ganglia with cirrhosis of the liver: 1) disorders of the liver and brain are simultaneous manifestations of the action of an endogenic toxin formed outside the liver; 2) primary lesion of the subcortical ganglia which regulate the functions of the liver; 3) cirrhosis of the liver is the primary, and lesion of the nervous tissue—the secondary disorder.

Some scientists believed that the disorder was caused by a toxin producing a relapsing interstitial hepatitis. Only after the function of the liver is impaired and it loses its capacity for neutralising the toxin does the latter penetrate into the general blood stream, causing nervous lesions. Certain facts speak in favour of a primary lesion of the liver. First of all, in Wilson's disease, as already stated

above, lesions are observed not only in the putamen, but also in other parts of the cerebrum, and occasionally even in the spinal cord. Changes in the nervous system may be produced by experimental lesions of the liver. There have been numerous descriptions of cases in which cerebral lesions were preceded by cirrhosis of the liver. As far back as in 1923, S. A. Chugunov observed a case in which cirrhosis of the liver preceded changes in the nervous system and emphasised the role of intoxication in the genesis of cerebral lesions. Later Dupérié, Maupetit and Dumen described the case of a girl of 12 years who was receiving treatment for splenomegalia diagnosed as Banti's disease. A severe intestinal haemorrhage and ascites were observed two years later. Splenectomy performed in connection with haemorrhagic diathesis revealed a contracted cirrhotic liver. The latter was confirmed by biopsy. Only six months later did symptoms of Wilson's disease appear. Djonys and Schroder observed a boy of 12 who developed rapidly the picture of an acute abdomen with fever, vomiting, xenthochromic sclera and urobilinuria. The presence of hepatosplenomegaly was observed; it remained after the acute abdomen symptoms had disappeared. Two years later, the lenticular degeneration syndrome became apparent after a brief spell of fever. The post-mortem examination confirmed the diagnosis of Wilson's disease.

The theory of the primary lesion of the liver was thoroughly elaborated by N. V. Konovalov who believes that the lesion of the nervous system is caused first and formost by the action upon the cerebrum of toxins engendered by the disintegration of hepatic parenchyma. The predominant lesion of the subcortical ganglia is explained, in N. V. Konovalov's opinion, by their specific morphological and functional features. These areas are the most vulnerable in disturbances of blood circulation in diseases of other etiology. The most abundantly vascularised regions of the brain with the largest amount of blood, they receive greater amounts of toxins which paralyse tissue

respiration. Furthermore, owing to the specific nature of their metabolism they are most sensitive to a blood supply deficiency.

When the barrier function of the liver is impaired, the blood receives an alien albumin which in its turn acts as a toxic agent.

Some authors have lately directed attention to disturbances of the copper metabolism in the organism in connection with hepatolenticular degeneration (Cummings, Uzman, Denny-Brown, Porter). An increased content of copper is found in different parts of the brain, liver and kidneys in persons affected with hepatolenticular degeneration. It has also been established that a considerable amount of copper is excreted with the urine (Mandelbrote, Cummings, Denny-Brown and Porter). Uzman and Denny-Brown found in addition a simultaneous increase in the excretion of aminoacids with the urine. However, Matthews and his collaborators did not find any increase in the aminoacid content in the blood and came to the conclusion that aminoacids act as alcalising copper agents. Brand and Takáts established that the pigment in the Kayser-Fleischer ring is also composed of copper.

Normally, the contents of copper in the blood fluctuates between 80 and 150 Mg per 100 ml. In hepatolenticular degeneration it drops to 40-60 Mg per 100 ml (Bearn, Kunkel). A considerable amount of copper is bound with blood globulins. Laurell and others isolated in 1947 α_2-globulin and copper complex which they called cerruloplasmin. Scheinberg and Gitlin found that cerruloplasmin disappears from the blood of patients suffering from hepatolenticular degeneration.

Especially striking in patients suffering from hepatolenticular degeneration is the seemingly contradictory fact of the simultaneous increase in copper deposits in the tissues and its excretion with the urine. Some of the latest investigations shed light on this contradiction. The source of copper deposits in the organism lies in its ingestion

from the gastrointestinal tract. By administering radioactive copper it has been found that in normal persons copper is captured by blood albumins, to be transferred within twenty-four hours from the albumins to the globulins. This transference is extremely slow, or is altogether absent, in patients suffering from hepatolenticular degeneration. Consequently, the organism is incapable of synthesising cerruloplasmin, in view of which considerable amounts of copper are deposited in the tissues and excreted with the urine. Zimdahl, Hyman and Cooke found that persons affected by hepatolenticular degeneration assimilate greater amounts of copper ingested with the food than healthy individuals do. They believe the higher assimilation of copper to be a reaction to the abnormally low content of cerruloplasmin in the organism.

On the basis of the mentioned investigations the conclusion may be drawn that the lesions of the subcortical ganglia and liver, and the appearance of the pigmental ring in the cornea are brought about by one cause, by disturbances of copper metabolism in the organism. Although some details remain to be clarified, there is convincing proof that the combination of seemingly independent, different lesions associated with hepatolenticular degeneration, have the same hereditary source of metabolic disturbances.

Until very recent years, any *treatment* of hepatolenticular degeneration was entirely hopeless. Establishment of the role of copper metabolism has prompted some scientists (Bearn and Kunkel, Denny-Brown and Porter, Cummings and others) to try BAL (British anti-lewisite; dimercaprol) which since the time of World War II was used as a remedy against intoxication with heavy metals, inasmuch as the containing sulfhydrate group of thiol binds the heavy metals and thus renders them harmless. The scientists observed a considerable improvement in the condition of their patients, although they emphasised that complete recovery could not be expected.

N. V. Konovalov and his collaborators administered unithiol (a Soviet preparation similar to BAL) in 18 cases of hepatolenticular degeneration. A considerable improvement was noticed in the condition of all the patients, and the conclusion reached was that treatment with thiol preparations is indicated in all forms of hepatolenticular degeneration. The discovery that ion metabolite resins can remove potassium from the organism prompted the use of natrium polystyrone sulphonate for the purpose of removing copper from the organism in cases of hepatolenticular degeneration.

HEPATIC COMA

Quite often cirrhosis and other diseases of the liver produce grave symptoms of intoxication of the nervous system which have long been known as hepatic coma. It has lately been demonstrated that symptoms of lesions of the central nervous system appear long before the coma, in the terminal stages of the disease.

Examining forty patients suffering from various diseases of the liver, without coma, Brown found in 65.5 per cent of these cases neurological symptoms, chiefly in the form of paresis, high tendon reflexes, pathological pyramid signs and tremor of the extremities. These signs are also observed after the formation of a portal anastomosis and in haemorrhages from varicose veins of the oesophagus connected with cirrhosis of the liver. Sherlock and others proposed to call this syndrome portal encephalopathy.

Headaches, apathy and insomnia sometimes precede the acute development of the disorder. In most cases, however, nervous symptoms develop acutely notwithstanding the relatively favourable, or compensated, course of cirrhosis. Rapidly oncoming drowsiness is combined with a shallow, uneven tremor of the extremities, the hands especially, with the constant flexion and extension of the extremities. These involuntary movements are intensified

by excitation and disappear in a state of complete rest. Muscular rigidity of the extremities is observed along with high tendon reflexes and Babinski's and Oppenheim's signs. In other cases attention is attracted by the contrast between the considerably increased tendon reflexes and the absence of pathological reflexes. Periods of excitation, delirium, and, in some cases, a state of stupor are observed frequently.

Given a benign course, these attacks last from 2 to 12 days. In rarer cases the attack passes into a deep coma with a fatal outcome.

Our own observation given below may serve as an example of portal encephalopathy.

Patient V., age 54, was hospitalised on September 27, 1957, with the diagnosis: post-operational status following hemorrhoidectomy; abscess, or tumour of the brain suspected.

From the information given by his wife and the abstract from the case history, it was known that the patient had attacks of malaria in his youth and that he was abusing alcohol. Enlargement of the abdomen, poor appetite, eructation and constipation were observed recently. On August 25, sharp pain appeared suddenly in the abdomen, and the patient was brought to hospital No. 40 with the diagnosis of ileus. Pain disappeared after syphon enema. Ligature of the hemorrhoids was performed on September 6. Motor excitation was observed on September 12; the patient began to utter senseless phrases, constantly trying to go somewhere. A sudden disturbance of consciousness on September 16 lasted 10-12 hours. The patient was disorientated, could not recognise anyone around him. A few days later his condition improved, but a confusional state recurred periodically and lasted 15-20 minutes.

Status at the time of admission: The patient of normal physique and satisfactory nutrition. Skin colouring normal. Bleeding gums. Lymphatic glands not enlarged. Oedema absent. Heart boundaries normal, tones dull. Pulse rhythmic, 105 beats per minute. Arterial pressure 140/80 mm Hg. Abdomen flatulent, sensitive to palpation, liver not enlarged. Urination normal.

Nervous system: Apathetic, inhibited, stunned, adynamic. Considers himself perfectly healthy. Answers to questions formally correct. Fulfils assignments with delay. Oral counting disturbed. Speech monotonous. Patters impossible. Names objects correctly. Pupils identical, reaction to light satisfactory. Nystagmus in glancing aside.

Slight sinistral hypoaesthesia of the face. The right nasolabial fold smoothened. No disturbances in swallowing, or phonation.

Paresis of the right hand and foot, muscular rigidity and pronounced tremor of the right extremities, tendon reflexes high, foot clonus, pathological reflexes absent, bilateral grasping reflex, sucking reflex and bilateral Kernig's symptom.

Eyeground normal. Lumbar puncture September 30: fluid colourless, transparent, pressure—240 mm, albumin 0.27 ‰, cytosis—1.

A certain improvement in the patient's general condition was observed on October 3: the patient was not as stunned and inhibited. On October 4, condition grave, the patient drowsy, dazed. When lifted, the right arm drops limply. Urination incontinence. On October 7, a slight improvement observed in the patient's condition, abdomen not as flatulent as before. October 9—the patient's condition grew worse again, pain in the abdomen reappeared. Abdomen flatulent, sensitive to palpation. Signs of ascites appeared. Venous network dilated in the anterior abdominal wall.

Blood count, November 28: Hb 70%, leukocytes 6,000, eosinophils 3%, band cells 1%, segmented cells 67%, lymphocytes 22%, monocytes 7%, erythrocyte sedimentation 65 mm per hour. Wassermann's reaction negative. Amount of bilirubin 1.25 mg%, reaction—direct. Weltmann's reaction—sharp shift of the coagulation column to the right. Takata-Ara reaction—sharply positive. On November 30, bilirubin 3.95%, reaction—direct. November 13, residual nitrogen—96%.

Urinary findings: Acid reaction, gravity 1,018, albumin 1.8 ‰, leukocytes cover densely the entire field of vision, erythrocytes 15 within the field of vision, urobilin test positive, diastase— 4 units.

November 1—abdominal puncture, 6.5 litres of ascitic fluid drained. Condition slightly improved. In the evening temperature 39° C., sensitiveness to palpation of abdomen. November 11—repeated haematemesis. November 12—incessant haematemesis.

November 13—severe deterioration of condition. Haematemesis. Eyeballs turned leftward. Pupils do not react to light. Lifted extremities drop limply. Tendon reflexes even. Pathological reflexes absent. Respiration—36 inhalations per minute. Skin subicteric, sclera xanthochromic. Moist rales of the lungs. Heart tones dull. Convulsive jerks of the extremities and face observed at the end of the day. Pronounced cyanosis, especially in the upper part of the body. Pulse—140 beats per minute, very weak. Arterial pressure 70/40 mm. Hg.

At 14 : 20, due to paralysis of respiration and cardiac failure, the patient died.

Clinical diagnosis: Atrophic cirrhosis of the liver, portal hypertension, ascites, varicose veins in the lower part of the oesophagus

with blood effusion, hepatic coma, myocardial distrophy, oedema of the lungs.

Pathological diagnosis: Atrophic cirrhosis of the liver, splenomegalia, varicose veins in the lower part of the oesophagus and cardial regions of the stomach, erosion of the venous walls with haemorrhages, multiple blood effusions in the viscera, subendocradial haemorrhages in the right ventricle, blood aspiration by the lungs, moderately expressed general atherosclerosis.

The pathological examination revealed a considerable hyperplasia of astrocytic glia in the brain, especially in the region of the striate ganglia.

N. V. Konovalov made a histopathological examination of the brain in four cases of acute and subacute toxic distrophy of the liver, 19 cases of various types of cirrhosis of the liver and one case of grave cholecystitis and cholangitis.

Changes resembling those in hepatolenticular degeneration were found in more than 50 per cent of these cases.

Only recently has some light been thrown upon the pathogenesis of nervous lesions in portal encephalopathy. Attention has been directed to a high content of ammonia in the blood of persons suffering from cirrhosis of the liver (McDermott, Adams, Sherlock and others). The normal content of ammonia ranges between 2 and 20 μg per 100 ml. In the case of a hepatic coma the ammonia content increases by 3-5 times. The intensity of the nervous symptoms in these cases depend upon the content of ammonia in the blood. McDermott and his collaborators found that nervous symptoms appear when the level of ammonia in the spinal fluid rises above 105 μg per 100 ml.

Ammonia is formed chiefly in the gastrointestinal tract. Normally, a considerable proportion of the ammonia circulating in the blood is transformed by the liver into urea. This function is disturbed by hepatic disorders. Increased content of ammonia in the blood impairs the synthesis of glutamic acid in the brain and depresses the respiratory capacity of the cerebral cells.

For the prevention of cerebral complications, persons suffering from hepatic disorders should be given adequate amounts of sugar and vitamins, especially vitamins C, K and the B group. When persons suffering from cirrhosis show symptoms of fatigue, confusional states and tremor, a protein-free diet is prescribed. Now that the pathogenic role of ammonia has been established, it is recommended to prescribe large doses of glutamic acid (Walsh).

It is also recommended to prescribe antibiotics (biomycin, levomycetin, terramycin and penicillin) for the purpose of suppressing the activity of intestinal microbes, and, consequently, for reducing the ingestion of nitrogen substances by the portal system.

MENINGEAL SYNDROME

The meningeal syndrome associated with severe hepatic insufficiency is described in a case of grave infectious jaundice. Meningeal symptoms are observed also in the terminal stage of cirrhosis of the liver. Four cases of cirrhosis of the liver accompanied by occipital rigidity, Kernig's sign, hyperaesthesia and high tendon reflexes observed in the terminal stage have been described. Meningeal symptoms were combined with a state of delirium, tremor of the extremities, motor disturbances and Cheyne-Stokes respiration. Tuberculous meningitis was suspected in one of the patients who suffered from tuberculosis. In all these four cases, no evidence of pleocytosis or hyperalbuminosis were found in the spinal fluid. Nor were any pathological signs revealed by the biochemical examination of the cerebrospinal fluid with the exception of an increased amount of polypeptides which was out of proportion with the residual nitrogen in the blood, or the amount of urea in the cerebrospinal liquor, or polypeptidemia. The authors explain the meningeal syndrome by intoxication with polypeptides which penetrate into the cerebrospinal fluid.

In one of our own observations of the meningeal syn-

drome in a case of cirrhosis of the liver we found symptoms of albuminocytologic dissociation in the cerebrospinal fluid which suggested the existence of oedema of the brain with disturbances of capillary permeability.

POLYNEURITIS

Polyneuritis associated with diseases of the liver were described by B. N. Mankovsky and L. I. Smirnov, and by M. A. Goldenberg. V. M. Slonimskaya believes that polyneuritis is observed in various disorders of the liver. In foreign literature cases of hepatogenous polyneuritis are described almost exclusively in connection with cirrhosis of the liver. Klippel and Lhermitte distinguish acute and chronic forms of this kind of polyneuritis.

The chronic form complicates the cachectic stage of cirrhosis. Nervous symptoms are confined mainly to motor disturbances. Sensorial disturbances are faintly expressed in this form, tendon reflexes are low, but do not disappear. Chronic, slowly developing forms of polyneuritis are observed in cases of cirrhosis complicated by ascites. The acute form of polyneuritis is observed in hypertrophic cirrhosis without ascites. It is accompanied by pronounced sensorial disturbances.

A mild form of polyneuritis developing directly from the initial stage of cirrhosis was described by Roger and other scientists. The patients complain of pain in the legs. An objective examination reveals a disappearance of patellar and Achilles tendon reflexes, sensitiveness of the muscles of the extremities to pressure, decelerated sensitiveness of the fingers and toes.

The connection of polyneuritis with diseases of the liver is proved by the parallel course of polyneuritis and cirrhosis. Some authors believe that polyneuritis is caused by a toxin from the intestines which is not detained by the impaired liver, or that hepatic insufficiency and polyneuritis may be caused by one factor. It is presumed that

this hypothetic factor may be a fluorescent substance, haematoporphyrin, for example. And yet, the direct connection between the hepatic disorder and polyneuritis remains unclear to this day. In the first place, the fact that polyneuritis is rare in hepatic disorders suggests the possibility of simultaneous action by other factors. It may be assumed that these types of polyneuritis should be classified among alcoholic, rather than hepatogenous disorders, because cirrhosis of the liver may often be of an alcoholic nature. The intensity of the two disorders varies. In some cases the neuritic symptoms recede far into the background in the picture of general cachexia connected with alcoholic cirrhosis, in other cases, in the pronounced forms of polyneuritis, there are only initial symptoms of cirrhosis. This fact prompts us to abandon the idea of direct dependence of polyneuritis upon the hepatic disorder.

It has already been proved that the origin of alcoholic polyneuritis is connected with Vitamin B_1 deficiency. As for the cases where the hepatic disorder is combined with polyneuritis, without evidence of alcoholism, avitaminosis is apparently also a pathogenic factor of polyneuritis. This is all the more probable, since achylia was also observed in the cases described hitherto.

Chapter VI

NERVOUS LESIONS ASSOCIATED WITH DISEASES OF THE KIDNEYS

AZOTEMIC URAEMIA

Azotemic uraemia is a clinical syndrome, developing due to an insufficiency of the secretory function of the kidneys. Azotemic uraemia may occur in subacute and chronic nephritis, in the terminal stage of contracted kidney, hydronephrosis, prostatic and cystic kidney, renal tuberculosis, syphilitic, amyloid kidney. Consequently, azotemic uraemia is not connected with a definite disease of the kidneys; it is the consequence of the terminal stage of various diseases, of renal insufficiency.

The cause of azotemic uraemia has not yet been completely established. Of great importance is the accumulation in the organism of final products of albumin metabolism. The subsequent intoxication of the organism develops slowly and gradually, and is accompanied by general weakness, impaired working capacity, inappetence and dull headaches. Patients complain of increased mental and physical fatigability and a sense of heaviness in the head. Apathy and somnolence develop gradually. The voice becomes feeble and soundless. Notwithstanding the heavy drowsiness, the patient cannot fall asleep. The complexion acquires a pale yellowish hue. Retardation of psychic processes and drowsiness lend the face a peculiar expression of melancholy, fear and a daze.

The state of stunning appears imperceptibly. The drowsy or soporous state is sometimes interrupted by excitation, insomnia, the patient tossing about in the bed, jumping up, trying to run. Confusional states appear in some cases, along with hallucinations, or excitation which passes into a maniacal state. However, the disturbances of consciousness are not constant, many patients preserving a clear consciousness until the very moment of death.

High excitability of the muscles in the form of jerks is observed at the height of the disease and frequently appears simultaneously with a picture of lethargy, stupor or even coma. They bear the nature of fibrillary and fascicular jerks, but they may also extend to large groups of muscles. Monoplegia, hemiplegia, aphasia and apraxia are sometimes observed. General and Jacksonian epileptic seizures are observed in rare cases. The paralyses in these cases are of a flaccid type, lasting several days, or hours, and then disappearing. Auditory impairment, giddiness and nystagmus are observed rarely.

In some cases, meningeal symptoms expressed in occipital rigidity, Kernig's and Brudzinski's signs appear in the early stage of the disorder. Pupils are often contracted, just as in the case of an experimental intoxication with urine. Hiccuping, vomiting, a depression of temperature are observed as the disorder develops, as well as intense Kussmaul's respiration which may pass into the Cheyne-Stokes respiration. It concludes with a deep coma.

The order in which the symptoms develop suggests the idea that the process spreads consecutively from the cerebral cortex to the deeper regions of the brain, until the disintegration of the vital centres in the terminal stage of the disorder brings on death.

Along with the development of the mentioned symptoms of central nervous lesions which occupy the leading place in the picture of uraemic intoxication, other symptoms of general intoxication appear, such as dryness of the tongue, ammiacal odour from the mouth with frequent develop-

ment of ulcerative stomatitis, vomiting appearing later together with diarrhoea. Scratches are found on the skin owing to incessant itching, and sometimes urea crystals on the face in the shape of fine branny spots become evident. Grave anaemia develops gradually, and dry pericarditis is added in the terminal stage. The urine is light-coloured, with low gravity and a high content of albumin and cylinders; indicanuria and in many cases also haematuria appear.

A picture of neuroretinitis is found in the eyeground; dilatation of the veins, engorged papillae and often blood effusions are apparent. These changes are not connected today with uraemic intoxication. They are observed in nephrosclerosis and chronic nephritis, and also in cases when the secretory function of the kidneys remains satisfactory.

Pressure of the cerebrospinal fluid is above normal; the fluid is transparent, xanthochromic in some cases, with a high amount of albumin. Monakow found considerable disturbances of the haematocephalic barrier and histopathological changes in the vascular plexus of the brain.

Some authors emphasise the fact that the albumin content in the cerebrospinal fluid increases. Monakow was seeking proof of disturbances of the haematocephalic barrier in changes of the vascular plexus. In two cases of contracted kidney with a marked increase of residual nitrogen he found histopathological changes in the form of flattened villose epithelium and decline of the number of villi, proliferation of connective tissue and hyaline substances between the capillaries and the epithelium. In Monakow's opinion, toxins circulating in the blood violate the integrity of the villi and reduce their normal protective function. In the cerebrospinal fluid Monakow found a considerable amount of urea, while the concentration of uric acid and creatinine in the blood and fluid was the same. Recent investigations revealed selective penetrability of the haematocephalic barrier with regard to specific sub-

stances. Concentrations of residual nitrogen, urea, creatinine and sugar in the cerebrospinal fluid proved to be higher than in the blood, while the concentration of uric acid, aminoacids and calcium was the same. It is rarely possible to find a positive xanthoprotein reaction in the cerebrospinal fluid.

During a pathological examination the meningeal membranes appear to be anaemic and oedematous. The irregular repletion lends the brain a marble appearance in slices. Histopathological changes in uraemia were described a long time ago. Various stages of degeneration of nerve cells in the cerebral cortex, pons and cerebellum were established. In the absence of inflammatory-proliferative processes, haemorrhages, perivascular oedema, lesion of the capillaries, an increase in the subendothelial connective tissue elements and necrosis of the muscular sheath of the blood vessels were found in the brain. At the same time diffuse changes were noticed in the ectodermal nerve elements in the form of ischemic and sclerotic changes of the nerve cells. Forms of uraemia should be classified according to the clinical picture. On the basis of this classification various changes are found in azotemic and eclamptic uraemia.

Characteristic of azotemic uraemia are numerous perivascular syncytial glia nodules, and giant neuroglia cells in advanced stages of the disease. Only small foci of red softening and circular haemorrhages are observed around the vessels.

Changes in the cortical cells are found practically in all cases. These changes differ in intensity and extensity. Bodechtel, Hechst and others described symptoms of chromatholysis chiefly in the fourth and fifth strata of the cortex. In other cases, lesions are much graver, expressed in vacuolisation, pyknosis and even in fatty degeneration (Weiman, Hechst).

The pathogenesis of uraemia is closely associated with intoxication caused by renal insufficiency, with retention

of products normally excreted with the urine, and, primarily, of urea, uric acid and aromatic substances which produce a xanthoproteinic reaction. Vidal and other representatives of his school believed retention of urea and uraemic intoxication to be the leading pathogenic factor in uraemia. According to the data of modern authors, there is no parallelism between the degree of retention of nitrogenous substances and uraemia. The level of residual nitrogen is not an indication of the gravity of uraemia, because considerable azotemia may be observed without uraemia, and, vice versa, a uraemic coma may occur without a considerable increase in the amount of residual nitrogen. The content of indican, phenol and aromatic acids changes in proportion to the gravity of clinical symptoms. However, they merely testify to the gravity of intoxication, and do not cause it. The nature of the toxins which cause uraemia remains unknown. A major part is played apparently by severe disturbances of albumin metabolism which condition acidosis in the blood of persons suffering from uraemia. The probability of complex intoxication is not excluded. Some investigators believe that acidosis and toxic disintegration of albumins are of decisive importance. Consequent hypoxemia of cerebral tissue leads to passive distension of the cerebral vessels and swelling of the cerebrum.

There is no difficulty in *diagnosing* azotemic uraemia in cases where anamnestic information is indicative of a chronic disease of the kidneys. Nervous symptoms stand out in the foreground in some cases and the fate of the patient depends upon the correct establishment of their cause.

Uraemia may be confused with general paralysis, other intoxications, or frontal tumours. In the case of persistent vomiting, headaches, confusional states and somnolence, the neurologist should not overlook the possibility of uraemia. He should take note of the ammiacal odour of the breath, the dry, scratched skin, thirst, signs of anaemia and gastrointestinal disorders. Deficiency

of the concentration function of the kidneys and increase of the residual nitrogen are important factors for discerning of azotemic uraemia.

ECLAMPTIC URAEMIA

Acute eclamptic uraemia occurs most often in glomerulonephritis and kidneys of pregnancy. It is rarely observed in cases of contracted kidney and sublimate kidney. Unlike genuine, azotemic uraemia, eclamptic uraemia does not depend upon disturbances of the excretory function of the kidneys. A major role is played in this case by high arterial and intracranial tension as well as circulatory disturbances in the brain. The latter may be general and local, they may develop acutely or gradually. Eclamptic attacks are often preceded by cerebral symptoms such as headaches, vomiting, impairment of vision and bradycardia. M. S. Vovsi reports about cases with pathological reflexes and high tendon reflexes at this period, considering affected persons "potential uraemics".

Most often eclamptic uraemia begins suddenly without any prodromal symptoms. A sudden epileptic seizure occurs in acute nephritis, sometimes even at the time when oedema subsides. Clonico-tonic convulsions last for several minutes and often reappear after a minute or two. During the attack the pupils are dilated and do not react to light. Babinski's sign is positive in many cases. As a rule, convulsive seizures occur rarely, but in some cases as many as 100-120 epileptic seizures a day may be observed. The attack may be of a Jacksonian type. Should the seizures reccur frequently, the patient may develop occipital rigidity and Kernig's sign. Amaurosis, hemianopsia, hemiplegia, psychic disturbances, dimness of consciousness, motor disturbances, and coma may remain after attacks, especially if they reappear frequently. Ordinarily, all these symptoms disappear, but the process of recovery may be long. Eclamptic psychosis expressed in excitation, a mani-

acal state, delirium and amentia are observed in rare cases. Paralysis, or choreiform hyperkinesia have been observed. Rudimentary forms, when the loss of consciousness occurs without convulsions, are rarer; dilated pupils, high tendon reflexes and pathological reflexes are observed in these cases. Arterial tension is always high. Ordinarily, the gravity of uraemic symptoms corresponds to the increase in arterial pressure, and a decline in this pressure is concomitant with the improvement in the clinical picture. Pressure of the cerebrospinal fluid is also higher than usual, the content of albumin in it is often increased, while the number of cellular elements remains normal.

Changes in the eyeground are associated with a considerable increase in the arterial pressure. Haemorrhages and white strips along the arteries (albuminuric neuroretinitis) are evident in the eyeground in grave cases. White spots resembling snowflakes, and sometimes stellar figures, are found in the region of the papillae and macula lutea. In some cases oedema of the papilla is highly pronounced, creating the picture of engorged papillae, just as in tumours of the brain. Unlike nephrosclerosis and secondary contracted kidney in acute nephritis and kidney of pregnancy, the appearance of neuroretinitis is not an unfavourable sign and it may disappear completely with the patient's recovery.

Post-mortem examinations reveal oedema of the brain with a considerable accumulation of liquid in the subarachnoid space. During the histological examination the perivascular spaces seem greatly extended. Circular haemorrhages are frequently observed in the brain; diffuse foci of large haemorrhages are found rarer. The circular haemorrhages consist of a round focus of fibrinous exudate and tissue necrosis around which the haemorrhage is located. Later, a marginal zone is formed of microglial elements. (Fig. 29.)

The *pathogenesis* of eclamptic uraemia is not quite clear to this day. Of decisive significance is the oedema of the

brain and angiospasm which causes an oxygen deficiency of certain regions of the brain. Increased arterial tension is not only a symptom; it is also a pathogenic factor. In the case of acute development of cardiovascular disorders, the predominant factor impairs the permeability of

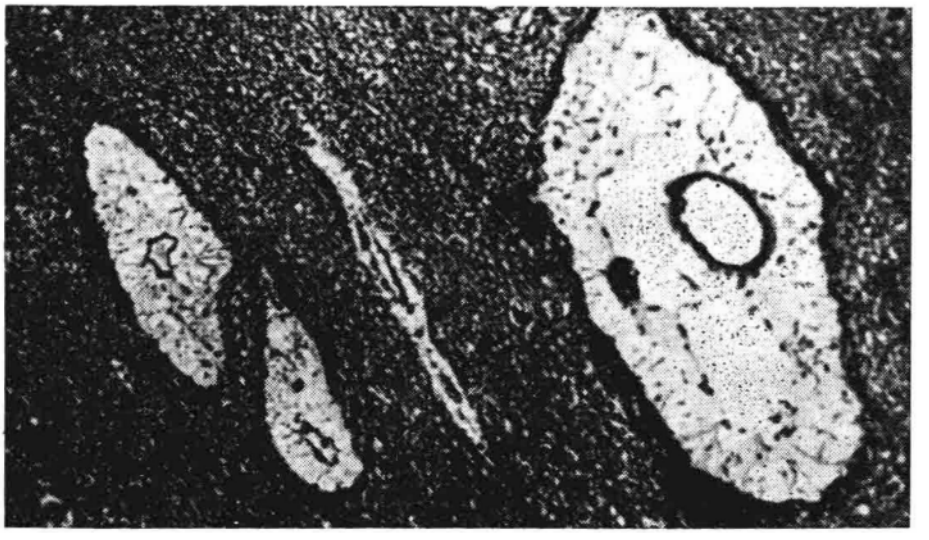

Fig. 29. Eclamptic uraemia. Distention of perivascular spaces in the cerebrum by serous fluid

the vessels and increases intracranial pressure concomitant with transient and localised anaemia in some regions of the brain. An attack is followed by marked venous stasis with an increase in the volume of the cerebrum which may become the source of a new attack.

There is nothing pathognomonic in the clinical picture of epileptic convulsions in eclamptic uraemia, and the diagnosis is therefore based on objective symptoms of renal disease and arterial hypertension.

Unlike azotemic uraemia, eclamptic uraemia begins acutely, rather than gradually. Epileptic seizures are very rare in azotemic uraemia, and arterial pressure may remain normal. The main differential diagnostic sign is the

presence of symptoms of azotemic intoxication in azotemic uraemia in the form of a high amount of residual nitrogen, respiration disturbances and the odour of ammonia.

The combination of headaches, vomiting, bradycardia, occipital rigidity and Kernig's sign may give the ground to suspect meningitis. Changes in the urine, oedema (facial oedema especially) and arterial hypertension furnish the basis for a correct diagnosis.

The prognosis in eclamptic uraemia depends upon the gravity of nephritis (mortality is up to 10-20 per cent). Should the patient survive, full recovery and the restoration of nervous functions may be expected.

Eclamptic uraemia should be treated in a hospital. In the first place, phlebotomy is employed (up to 400-500 ml) and intramuscular injections of 25 ml of a 25% solution of magnesium sulfate. An enema with 1-1.5 g of hydrate of chloral is prescribed in the case of repeated eclamptic seizures. A lumbar puncture may prove useful in some cases. An intravenal injection of 30-40 ml of a 40% solution of glucose is recommended. Reserpine, or serpasil, may be prescribed in doses of 0.25 mg three times a day for lowering arterial pressure.

PARALYSIS IN RENAL HYPERKALIEMIA

Cases of renal insufficiency attended with muscular paralysis, caused by the retention of potassium in the organism (hyperkaliemia) have recently been described. Eight cases of renal insufficiency with hyperkaliemia and muscular paralysis were described by Finch and Marchand in 1943. Mollaret, Goulon and Tourkilhac collected 14 cases in literature and added three of their own observations.

Muscular paralysis was observed in cases of glomerulonephritis, tuberculosis of the kidneys and cystic kidneys. Muscular paralysis developed in the period of pronounced renal insufficiency, in the presence of anuria, or oliguria. Paralysis develops within a few hours, and rarer, within a

few days. They may disappear rapidly when the patient's condition improves. The first to be affected are the muscles of the lower extremities, but before long the paralysis extends to the upper extremities as well. In some cases, respiratory disturbances are caused by paralysis of the respiratory muscles. Muscles innervated by cranial nerves are often affected. The paralyses are of a flaccid nature, accompanied by low muscular tone, the tendon reflexes being low or disappearing altogether. Mechanical excitability of the muscles remains intact.

Paralyses often begin with paraesthesia in the lower extremities. Objective sensorial disorders are very rare.

The paralysis is accompanied by a 3-fold or 4-fold increase in blood potassium (normal content amounts to 140-200 mg/l). The cerebrospinal fluid remains normal. In histological examinations made in two cases, Finch and Marchand, failed to find any changes in the nervous system.

It may be that the rarity of paralysis in renal insufficiency is relative. It appears in a stage of the disease when it may be overlooked due to the patient's grave condition.

The diagnosis is based on a high content of potassium in the blood and a specific electrocardiogram: increased T deflection, downward shift of the S-T interval, elongated P-R and QRS intervals, decline and disappearance of the R deflection.

Apart from the usual means of treatment employed in renal insufficiency, it is necessary to reduce as far as possible the intake of potassium with the food. It is recommended to prescribe intravenal administration of a hypertonic solution of glucose which assists in the transmission of potassium from the blood plasma into the cells of the organism, on the one hand, and, on the other hand, it inhibits nitrogen catabolism which tends to increase kaliemia. The paralysis is attenuated by the intake of calcium.

Chapter VII

NERVOUS LESIONS ASSOCIATED WITH ENDOCRINE AND METABOLIC DISORDERS

THYROTOXICOSIS

The clinical picture of diseases of the thyroid gland, just as of other endocrine glands, is not infrequently expressed in a number of nervous symptoms, especially in the initial stages of the disease. This is explained by the close functional connections between the nervous system and endocrine glands. It is impossible to cover the specific clinical pictures and pathophysiology of disorders of the thyroid gland within the limits of this book. It will therefore be restricted to the symptoms and syndromes caused by secondary nervous lesions which by their clinical picture may be mistaken for a primary disorder of the nervous system.

Among the main complaints with which persons suffering from thyrotoxicosis often come to the neurologist is exophthalmus. In some cases exophthalmus is limited to one eye, or begins on one side. In such cases thrombosis of the cavernous sinus, aneurysm of the internal carotid artery and a retrobular tumour should be excluded. Protrusion may hinder the movement of the eyes. A true oculomotor paralysis is exceptionally rare, and it may be followed by diplopia, chiefly owing to paresis of the m. superior rectus.

According to I. B. Khavin, muscular weakness is observed in 55 per cent of the persons suffering from thy-

rotoxicosis. Patients complain that their legs give way under them when they are walking and that they can lift their extremities with difficulty. In some cases muscular weakness appears paroxysmally and the legs give way suddenly when the patient is walking. In rare cases attacks of muscular weakness resemble attacks of paroxysmal myoplegia which makes them pathogenically close to familial paroxysmal paralysis.

World literature contains descriptions of about 50 cases of paroxysmal myoplegia associated with thyrotoxicosis (Linder). In some cases thyroidectomy resulted in a complete recovery. Our following observation may serve as an illustration:

Patient F., 37 years of age, was brought to the neurological department of the Botkin Hospital on October 16, 1940, with complaints of high irritability, palpitation and periodic paralysis of the extremities.

He had rheumatism in childhood and typhus at the age of 17. The present disorder began in April 1939, when on awakening one morning he felt a sudden drastic weakness in the arms and legs which kept him in bed. This condition lasted for about 20 minutes, whereupon the feeling of weakness passed away gradually. He managed to rise and walk independently; only a slight feeling of general weakness was left.

The same attack recurred in the morning of the following day, and several similar attacks were observed in May. In December of the same year, an attack began in the theatre and the patient could not rise from his seat. A few minutes later he managed to stand up, but he walked with difficulty, conscious of uncomfortable sensations in his legs. Since then, paralytic attacks recurred many times during the month, chiefly at night, or in the morning after sleep.

Status praesens: Nutrition subnormal. Moderately pronounced exophthalmus with positive Graefe's and Möbius' signs. Objective signs of organic lesions of the nervous system absent. Marked tremor of the hands, eyelids and head. Thyroid gland diffusely enlarged. Heart boundaries normal, tone dull. Pulse rate 120 per minute. Arterial pressure 130/70 mm Hg. Profuse sweating. Blood count and urinary findings without deviation from normal. Basal metabolism +37%. Blood potassium 22.6 mg%, calcium 11.3 mg%, chlorine 369 mg%, sugar content 97 mg%. An attack began in the night of

October 17. Results of examination during the attack: consciousness clear, speech not disturbed, cranial nerves normal. Flaccid paralysis of all the extremities with the disappearance of tendon reflexes and electric excitability of muscles. Sensorial disturbances absent. Sphincter functions normal. The attack lasted for 1 hour 20 minutes.

In November, the patient was transferred with the diagnosis of Basedow's disease to the Endocrinological Institute where a thyroidectomy was performed in February 1941. Attacks of myoplegia disappeared completely after the operation and did not reappear for 12 years during which he was under our observation.

The combination of hyperthyreosis and periodic paralysis is observed quite often and it affords the ground for ascribing to thyrotoxicosis a pathogenetic role in conditioning periodic paralysis in some cases. If thyroidectomy leads to the disappearance of periodic paralysis as well as of thyrotoxicosis, then the logical conclusion should be that thyrotoxicosis calls forth the metabolic disorder, which in its turn conditions attacks of periodic paralysis. Periodic paralysis is apparently not only a specific hereditary familial disease, but also a syndrome which appears in different diseases, including thyrotoxicosis.

It has lately been established that attacks of periodic paralysis are caused by disturbances of potassium metabolism in the organism. Hyperglycaemia induced by a high amount of carbohydrates in the diet, injections of insulin, or adrenalin, may call forth an attack. The pathogenic connection of periodic paralysis with thyrotoxicosis is not sufficiently clear as yet. Thyrotoxicosis is often accompanied by hyperglycaemia. It is possible that a significant part is played by intensified production of adrenalin and hypersensitiveness to it in thyrotoxicosis. Even a single injection of thyrotoxin may stimulate a hypersecretion of epinephrine by the adrenal glands. A hypersensitiveness of many organs to adrenalin is also known to be produced by the action of the thyroid hormone.

Thyrotoxicosis rarely causes muscular atrophy resembling that in myopathy. D. I. Friedberg notes that muscular

weakness and atrophy are observed only in the proximal parts of the extremities. Ross and others described three cases and collected in literature ten cases of "chronic thyrotoxic myopathy". They direct attention to the fact that this syndrome is observed in elderly men and is characterised by progressive loss of weight, weakness, atrophy and, in some cases, by pseudohypertrophy of the brachial and pelvis muscles. Creatinuria is one of the symptoms observed in these cases. Thyroidectomy leads to complete recovery.

A symptom characteristic of thyrotoxicosis is tremor of the extremities which sometimes extends to the head and trunk. The shallow, frequent tremors (8-10 per minute) are intensified by motion, excitement and fatigue. The combination of tremors with a sebaceous face and amimia may suggest the idea of parkinsonism. Tremor in parkinsonism is larger, it tends to grow at peace and is attended by muscular rigidity.

Growing tumours of the thyroid gland may bring about compression of the nerves on the neck. Hoarseness produced by compression of the n. recurrens is often observed, along with Horner's syndrome and increased perspiration of the face. Compression of the nerves in the neck may cause pain. Lastly, it should be borne in mind that carcinoma, adenocarcinoma and struma metastaticum may metastasise into the cranial and vertebral bones and produce a picture of a cerebral, or cerebrospinal tumour. These metastases may be hormonally active. In this case their location may be determined by means of radioactive iodine.

HYPOTHYROSIS AND MYXOEDEMA

Nervous symptoms are most significant in hypothyrosis and myxoedema in adult persons. Patients complain of rapid physical and mental fatigability, apathy, inertia, somnolence and of the impossibility to concentrate attention. Attacks of fear and schizoid reactions are observed

in some cases. Pain in the lumbar region and extremities, stiffness of the back and extremities may be felt at the beginning of the disease. Appearance of the above-mentioned symptoms suggests the idea of hypothyrosis which is often overlooked, especially in elderly women. These patients are often being unsuccessfully treated for neurasthenia, avitaminosis, neuritis, spondylitis, or diencephalic syndrome. Retarded psychic processes and impairment of memory give ground for the erroneous diagnosis of cerebral atherosclerosis.

The diagnosis of myxoedema is based on other symptoms of the disease: puffiness of the face and eyelids, dryness and roughness of the skin which is sometimes tinted yellow due to deposits of carotene, enlargement of the tongue and larynx which makes the voice hoarse and low. The pulse decelerated, arterial pressure low, and the amount of cholesterin in the blood high. Other symptoms are the loss of hair on the head and eyebrows, constipation, meteorism, hypersensitivity to cold. There is a high amount of albumin in the cerebrospinal fluid.

Adynamia, muscular pain and cramps are sometimes combined with muscular hypertrophy, or pseudohypertrophy. There are also descriptions of a pseudomyotonic syndrome (Lambert and others), which, in addition to muscular hypertrophy, is characterised by slow, athetose contraction of the muscles in response to stimulation by an electric current, but, after active contraction, the muscles do not relax gradually as in myotonia.

PARATHYROID HYPOFUNCTION (TETANY)

Tetany is observed most frequently after operations on the thyroid gland, in the case of accidental injury of the parathyroid glands. Idiopathic tetany is much rarer. Complete parathyroidectomy may be followed by general tetanic attacks with muscular spasm, laryngospasm and subsequent coma.

Nervous symptoms occupy a big place in the clinical picture of chronic parathyroid insufficiency. The main symptom is high neuromuscular excitability which in latent cases is recognised by the following characteristic signs. Tapping on the muscles in the region of the exit of the facial nerve from the canal produces homolateral spasm of the muscles of the face, eyes and mouth (Chvostek's sign). Pressure upon the brachial muscles produces convulsive contraction of the muscles of the wrist and fingers (Trousseau's sign).

In more pronounced forms of the disease muscular spasm begins spontaneously. The patient's hand assumes the characteristic position known as accoucheur's hand. The foot adopts the position of pes equinus. Episthotonos, masseter spasm, strabismus blepharospasm and glossospasm are observed in some cases. In rarer cases we find spastic contractions of the smooth muscles: laryngospasm with dyspnoea, polyrospasm, intestinal colics and ileus.

The disease begins with drawing pain and paraesthesia in the extremities. Excitability of the sensory nerves is increased considerably. Mechanical and thermal irritations cause pain. The nerve trunks are sensitive to pressure. Stable muscular spasms are very painful.

The protracted course of tetany is followed by trophic disturbances. The skin becomes dry and pealing, the hair—breakable and dry, cataracts developing in some cases.

Psychic disturbances are most frequently expressed in attacks of fear and premonitions of approaching disaster. Depression is sometimes observed; visual and auditory hallucinations appearing in grave cases. Maniacal, or depressive, psychosis, with confusional states and delirium are observed in rare cases.

Intracranial hypertension is quite frequent, but it is usually of a latent nature, expressed in dilatation of the veins of the retina and engorged papillae. Severe headaches are rarer. A lumbar puncture reveals hypertension in the

cerebrospinal fluid. In children an *X*-ray examination of the cranium may reveal a disunion of the sutures of the skull.

Pick discovered in cases of tetany intracerebral deposits of lime. There is proof of the connection between these deposits and parathyroid insufficiency. Ordinarily lime deposits do not manifest themselves clinically and they are found only by means of *X*-ray examinations. Anatomical examinations usually reveal them in the subcortical ganglia, dentate nucleus of the cerebellum, in the cerebral cortex and cerebellum. Lime is deposited also in the adventitia and tunica media of the minor arterioles.

Establishment of the tetany syndrome, even when there is a low content of calcium in the blood, does not yet provide a complete solution to the diagnostic problem, because only in some cases does the disease depend upon the insufficency of the parathyroid glands. Calcium deficiency may be caused by disturbances of ingestion from the intestines, or by the loss of calcium in diarrhoea, due to chronic intestinal disorders, sprue especially.

Symptoms of tetany may also develop in the case of an increased requirement of the organism for calcium and its deficiency in the food, or its poor assimilation owing to Vitamin D_2 deficiency (in children affected by rickets, or in pregnant women).

Tetany with a normal content of blood calcium is caused by alcalosis, most frequently in diseases associated with protracted vomiting and loss of hydrochloric acid (gastric tetany). Analogous in principle is the mechanism underlying the development of tetany in hyperventilation. Accelerated deep breathing leads to the rapid development of respiratory alkalosis. The picture of hyperventilation tetany may be observed in persons with vegetative lability and persons affected by thyrotoxicosis in a state of excitation and fear connected with intensified respiration.

Central Regulation of Carbohydrate Metabolism and Neurogenous Diabetes. When, in 1854, Claude Bernard made his "sugar puncture" in rabbits, in the region of the vagus nucleus at the bottom of the IV ventricle, he initiated a series of numerous studies of nervous regulation of carbohydrate metabolism. Lewy and others found that irritation of the posterior region of the dorsal nucleus of the vagus produces hyperglycaemia and glycosuria, while irritation of the anterior part of this nucleus produces hypoglycaemia. On the basis of these investigations the authors reached the conclusion that it is a question of two antagonistic centres, the anterior and parasympathetic, which act upon the pancreas through the vagus, and posterior sympathetic directed towards the adrenal gland. After tracing the retrogressive degeneration of nerve fibers in a sugar puncture, the same authors established the existence of a carbohydrate metabolism centre in the paraventricular nucleus of the diencephalon. The latter was confirmed by the works of other authors. Dresel and Lewy acknowledge also the existence of another centre located higher, in the globus pallidus.

The nerve formations which regulate carbohydrate metabolism are controlled by the cortical cells of the premotor area. The assertion concerning the existence of all these centres was subjected to serious criticism (A. A. Bogomolets). Experimental investigations conducted by Hiller and his collaborators also speak against the strict localisation of these centres. There is no doubt, however, that in juries of definite regions of the brain cause changes in carbohydrate metabolism. It has been established that there are direct connections between the hypothalamus and medulla oblongata and the organs regulating the carbohydrate metabolism. Some investigations have shown that glycosuria produced by sugar puncture may not appear if a

preliminary discission of the spinal cord is made in the cervical region, and after an extirpation of the nn. splanchnici and extirpation of the adrenal glands is performed. It has thus been demonstrated that the paths from the vegetative centres lead through the spinal cord to the nn. splanchnici, towards the adrenal glands the hormone of which exerts diastetic action upon liver glycogen and changes the sugar content in the blood and urine.

Other authors have shown also that a sugar puncture may produce favourable results after the extirpation of the adrenal glands; that is indicative in the direct connection of the vegetative centres with the liver. Davis and others destroyed the hypothalamus in animals without injuring the hypophysis. Resection of the pancreas did not produce diabetes in animals which had undergone this operation. Investigations conducted by these authors showed that irritation of the anterior hypothalamus mobilises carbohydrate reserves by stimulating the adrenal system, while the impairment of the paraventricular nuclei raises sensitiveness to insulin.

Barris and Ingram produced disturbances of carbohydrate metabolism by destroying the hypothalamus. They believe that the hypothalamus controls the anterior part of the hypophysis which plays an essential part in the regulation of carbohydrate metabolism. Complete extraction of the hypophysis does not produce glycosuria, if the hypothalamic region is not injured. Hypophysiectomy produces glycosuria in dogs only when the bottom of the III ventricle is destroyed.

Hussey found that the gravity of diabetes following the extirpation of the pancreas may be considerably attenuated by removing the anterior lobe of the hypophysis. That is explained by the disintegration of the diabetogenic hormone secretion which is necessary for the appearance of hypoglycaemia after the extirpation of the pancreas. Davis, Cleveland and Ingram found that a similar effect is produced by injury of the hypothalamus. On the basis of

these experiments it may be assumed that secretion of the diabetogenic factor is regulated by the hypothalamus.

Glycosuria is often observed in various organic lesions of the cerebrum: traumatic injuries, tumours, cerebral haemorrhages, as well as subarachnoic haemorrhages and encephalopathy. The sugar content in the blood and urine is often increased after brain injuries. Sugar in the blood is often increased without glycosuria. This high sugar content may continue for three weeks, but it is usually of a transient nature. Glycosuria may also be observed after injuries of other parts of the body, but as a rule it is higher in cerebral injuries. We have observed glycosuria in cases of craniopharyngioma. All these facts are indicative of the role played by the central nervous system in carbohydrate metabolism, but they do not solve the problem of the neurogenic origin of diabetes.

Regarding the neurogenic origin of diabetes, we can mention a far smaller number of thoroughly checked observations. It is possible that diabetes insipidus passes into diabetes mellitus owing to lesions of the paraventricular nucleus. B. N. Mogilnitsky reports about a few of his own observations of haemorrhages and bullet wounds of the neostratum with subsequent severe diabetes. Morgan found cellular atrophy of the paraventricular nucleus in diabetes mellitus. Diaz believes that the difference between neurogenous diabetes and pancreatic diabetes lies in the glycogen deficiency in the pancreatic form (in the liver especially). Neurogenous diabetes, on the contrary, is marked by the more rapid disintegraton of glycogen rather than by its insufficient formation.

Here is one of our observations.

Patient K., age 13, was brought to the hospital on December 19, 1938, with complaints of pain in the abdomen, vomiting and excessive thirst. In the summer of 1938 she injured her head and lost consciousness for twenty-four hours. Since then she was tormented by thirst. Her "legs and abdomen ached" throughout the autumn.

Status praesans: Marked general emaciation. Skin dry and

smooth. Dull bruit heard under right lung apex on percussion. Short, flapping tones of the heart. Electrocardiogram: highly pronounced sinus arrhythmia with brachycardia, the deflection T is smoothened throughout the complex. Sugar content in the blood—350 mg%, sugar in the urine—5.4 mg%. Symptoms of organic lesions of the nervous system absent. Insulinotherapy combined with diet brought about a tolerance of carbohydrates received in amounts ranging up to 200 g a day. The patient gained 9.5 kg in weight, sugar disappeared from the urine and blood sugar dropped to 128-158 mg%. After being discharged from hospital she was receiving insulin treatment until the middle of July 1939. On August 3, 1939, her condition took a drastic turn for the worse. In the evening of the same day the patient was brought to the hospital in a state of coma with Kussmaul's respiration; pulse rate 96 per minute, marked acetone odour from the mouth. Died two hours later.

Anatomic diagnosis: Diabetic coma, hyperaemia and oedema of the lungs, focus of tuberculosis in the left lung, ischemic foci in the liver, cyst in the hypothalamic region.

Histological examination: The cyst is lined with ependyma, the walls being composed of glial elements. Cells of the vegetative nucleus type characteristic of the hypothalamic region may be seen in the walls of the part of the cyst adjoining the infundibulum. A large area in the hypophysis is composed of basophilic cells with marked oedematic infiltration and loosened tissue. In the remaining part of the hypophysis there is a considerable amount of basophilic cells and some main cells. Many Langerhans islands in the pancreas are of a normal type. Marked fatty infiltration of the kidneys.

In the mentioned case, the development of diabetes following cranial injury, discovery of a cyst in the hypothalamic region, with the pancreas in a normal state, make it possible to speak of central diabetes; but even this case cannot be taken as absolute proof. Consequently, the opinion on the question of the neurogenous mechanism of diabetes mellitus considered correct to this day is that the cerebral origin of true diabetes has not been thoroughly checked, but that according to all available information changes in the diencephalon may contribute to the appearance of the disease.

Nervous Lesions in Diabetes Mellitus. Describing cerebral lesions in diabetes, Hartmann and Schrottenbach directed attention primarily to headaches, giddiness and in-

somnia. These authors speak of oculomotor disturbances and lesions of other cranial nerves which usually appear suddenly. There are also descriptions of epileptic seizures (not only in a state of coma) and various symptoms of focal lesions of the cerebrum. It may now be accepted as an established fact that these symptoms are conditioned by concomitant diseases: atherosclerosis, hypertensive disease or syphilis. This applies to a still greater degree to old haemorrhages and cerebral softenings. Reference is made to cases in which the disorder was accompanied by arteriosclerosis or the hypertensive disease. About 48 per cent of persons suffering from diabetes mellitus die of arteriosclerosis (including 7% of deaths from cerebrovascular accidents).

An essential factor in diabetes is the predisposition to degenerative processes and infections. Diabetic retinitis and atrophy of the ophthalmic nerves are observed in some cases.

The pathogenesis of diabetic amblyopia has much in common with that of amblyopia alcoholica. An essential factor in it is apparently the deficiency of the Vitamin B complex.

The sugar content in the cerebrospinal fluid corresponds to its concentration in the blood (normal ratio). Acetone may be found in the fluid in a precomatose state, and acetic acid is found in the fluid only in cases of grave coma. In protracted ketonuria, ketonic bodies pass into the fluid (L. A. Kostakov).

The most dangerous complication in diabetes is the hyperglycaemic coma. It is caused by the accumulation of products of the metabolism of fatty acids: β-hydroxybutyric acid, acetic acid and acetone. Disturbances of carbohydrate metabolism render impossible the oxidation of lipids and of albumins to their normal products of disintegration. In order to meet the required demand for energy the organism has to use a great amount of albumins and lipids. Moreover, it loses the capacity for further com-

bustion of ketonic bodies, which leads to their accumulation in the organism and to the development of acidosis. Accumulated in the organism, β-oxybutyric acid acts as a toxic agent upon the central nervous system. In the opinion of S. S. Geness, β-oxybutyric acid depresses fermentation processes in the central nervous system and deprives its cells of normal nutrition. Severe biochemical disturbances may cause disintegration of cell albumin and the consequent release of considerable amounts of potassium and phosphates which are excreted with the urine.

A state of coma may be caused by the termination of injections of the customary dose of insulin, faulty diet, infectious disease, or psychogenic trauma. In most cases, a diabetic coma develops gradually, within a few days. It begins with gastrointestinal disorders such as inappetence, pain in the abdomen, nausea, vomiting, constipation, or diarrhoea. They are followed soon thereafter by a feeling of general exhaustion, apathy and headaches. Respiration becomes difficult, the breathing deep and slow (Kussmaul respiration). The odour of acetone is felt in the breath. The patient is in a state of prostration, followed by a soporous state which passes into a deep coma. The pulse becomes very weak and frequent, the temperature is normal, or subnormal, arterial pressure falls. The pupils are dilated. Tendon reflexes are decreased or absent, the muscular tone is low. In the subsequent general intoxication of the organism the leading part is played by poisoning of the central nervous system which accounts for the respiration disturbances, vascular collapse, low muscular tone and disorders of the higher nervous system.

Histopathological changes found in the brain resemble those observed in general asphyxia. The vessels are dilated, and are in a state of stasis. Disturbances of capillary permeability leads to oedema of the brain and to the destruction of the nerve cells owing to metabolic disorders and great sensitiveness of these cells to the oxygen deficiency.

Three types of lesions of the spinal cord have been described.

1. Changes in the motor cells of the anterior horns of the spinal cord and in the cerebral trunk. In some cases, chronic poliomyelitis was observed in the clinical picture. In most cases it was not established whether these changes were primary or secondary, owing to changes in the nerve roots and peripheral nerves.

2. Degeneration of the posterior nerve roots and columns resembling changes in tabes dorsalis. It has long been known that a syndrome resembling tabes dorsalis (pseudotabes diabetica) may be observed in diabetes. Contemporary authors believe that this syndrome in diabetes is caused by lesions of the peripheral nerves.

3. Degenerative changes in the posterior columns and, to a lesser degree, in the lateral ones, resembling the picture of funicular myelosis in Biermer's anaemia. Griggs and Olsen who described a similar case believe that contraction of the vascular lumen and thickening of the vascular walls conditioned a prolonged insufficiency of blood supply to the spinal cord which resulted in the pathological changes in it. We have observed a 57-year-old patient who suffered from diabetes for 30 years. In 1931, the disorder was exacerbated by symptoms of polyneuritis. A trophic ulcer of the foot developed in 1934. That was followed in 1939 by the subacute development of the picture of transverse myelitis. The post-mortem examination revealed necrosis of the thoracic segments of the spinal cord. Arteriosclerotic changes, without any indications of syphilis, were found at the histological examination.

Spinal lesions are rare in diabetes. Woltman and Wilder collected in literature 42 cases of diabetes in which histopathological examinations of the spinal cord were made. Changes in the spinal cord were found in twenty of these cases. The authors emphasise that most of these cases were described before the Wassermann test was applied,

while the anatomical picture gives no grounds for the complete elimination of syphilis.

Diabetic polyneuritis affects almost exclusively the lower extremities. Some authors believe that polyneuritis may be observed in more than 50 per cent of the cases of diabetes, others find it in less than one per cent of the patients suffering from this disease. This marked discrepancy is explained by different approaches of the authors to the definition of diabetic polyneuritis. Some believe that all cases in which patients complain of pain, should be classified as polyneuritis even in the absence of objective signs (Jordan, Barach). Others classify among polyneuritis only those cases where objective symptoms are evident. On the basis of this strict selection, Rundles found in 400 patients with diabetes four per cent of the cases with polyneuritis. Martin observed objective symptoms of polyneuritis in five per cent of the cases of diabetes, while 12 per cent of the patients complained of paraesthesia and pain, although no objective symptoms were found in them. As a rule, long before polyneuritis appears it is preceded by prolonged diabetes which is poorly treated or overlooked altogether.

More frequently observed are the abortive forms of polyneuritis, which are often expressed in isolated symptoms: muscular pain, paraesthesia, disappearance of tendon reflexes and trophic disorders. Pain in the legs, appearing as an isolated symptom, is localised in the m.gastrocnemius, although in most cases objective examinations do not reveal any disorders. Complaints are often made of burning sensations in the toes and feet owing to paraesthesia, its intensity growing at night. Cooling of the feet brings relief (diabetic causalgia). Lastly, isolated disappearance of patellar and Achilles tendon reflexes is observed very often.

Diabetic polyneuritis develops gradually, and in rare cases—subacutely. Progressing slowly, it may begin with neuralgia of specific nerves: the ischiatic, femoral, or the

brachial plexus nerves. Noteworthy of the development of diabetic neuralgia is the tendency towards symmetric lesions, as, for example, bilateral neuralgia of the ischiatic nerve. Neuralgia of the femoral nerve is observed quite often; therefore, this kind of unilateral, and, especially, bilateral neuralgia gives ground to suspect diabetes.

Already at the end of the last century, Leyden singled out three basic forms of diabetic polyneuritis, sensorial, motor and atactic forms. Subsequent investigations revealed that the sensorial form, with protracted dull pain rarely developing into shooting pain, is most conspicuous and characteristic of diabetes. In most cases the pain is localised in the legs, chiefly in the m. gastrocnemius. This pain usually becomes more intense at night. It may be an incessant pain, intensified in some cases by paroxysmal developments.

In more than 50 per cent of the cases, pain is combined with paraesthesia expressed in burning, prickling, numbness and formication. Objectively, sensorial disturbances are expressed primarily in disorders of vibratory sensations. Sensorial disturbances of all types in distal regions of the lower extremities are rare. Most frequently observed among other symptoms of the sensorial form of diabetic polyneuritis is the disappearance of tendon reflexes, and of the Achilles tendon reflexes in the first place. There are descriptions of cases in which this kind of polyneuritis is combined with symptoms of retrobulbar neuritis of the ophthalmic nerves.

In the so-called motor form, sensorial disturbances are combined with muscular weakness and atrophy, most often in the extensors of the feet, and sometimes in the quadriceps femoris.

The atactic form is distinguished by moderate paresis of the legs, pronounced ataxia in them, deep sensorial disturbances and disintegration of tendon reflexes. Trophic disturbances in the form of a perforating ulcer of the

foot are found in this form. It is sometimes observed also as an isolated symptom.

There are descriptions of a few cases of polyneuritis with albuminocytologic dissociation in the cerebrospinal fluid. In such cases, severe pain in the extremities is combined with paralysis, grave sensorial disturbances and albuminocytologic dissociation in the cerebrospinal fluid. Lesions of the cranial nerves are rare. Martin found these lesions in four out of 150 cases of diabetic polyneuritis. Available descriptions deal mainly with paresis of oculomotor and facial nerves.

The pseudotabes diabetica syndrome is observed in some cases; it includes the disintegration of tendon reflexes with deep sensorial disturbances, shooting pain in the arms, arthropathy and trophic ulcers. Contraction of the pupils and their weak reaction to light are observed in some cases.

Attention has lately been directed to signs of involvement of the vegetative nervous system (Rundles, Treusch and Martin). They are expressed in moderate oedema around the malleoli, in the absence of diseases of the heart, kidneys, varicose veins, or other reasons for this oedema. Absence of perspiration of the feet, the atrophy of the skin and trophic disorders in the nails are also noted. On the basis of his investigations Martin reached the conclusion that vasomotor disturbances, as well as disturbances of perspiration, are observed in all cases of diabetic polyneuritis and also in cases where pain in the legs is found in the absence of objective symptoms.

Some authors (Rundles and others) emphasise that while gastrointestinal disorders are observed equally often in diabetics, as well as in patients who are not affected with this disorder, diabetic polyneuritis is often combined with constipation, attacks of diarrhoea at night or in the morning. Neurogenous atonia of the bladder with urine retention may be observed in some cases, and, in rarer cases, with ischuria paradoxa.

Complaints of impotence were quite frequent, but they

have greatly diminished following the administration of insulinotherapy. Rundles emphasises the frequency of impotence in diabetic polyneuritis. In one-third of the number of patients affected by impotence in polyneuritis, Martin found urinary disturbances and arrived at the conclusion that these symptoms depend upon lesions of the sacral vegetative nerves.

Histopathological examinations reveal primary degenerative changes of the peripheral nerves which are more pronounced in the peripheral nerve itself than in its roots.

A characteristic picture is observed of segmental periaxial neuritis in which the nerve fibers are intact, while their myelin sheath disintegrates into separate globules and drops. In that case Schwann's sheath becomes swollen, the perinuclear part of the cytoplasm is infiltrated and darkly coloured, the appendage of the Schwann cells enveloping the elements of disintegrated myelin. The nerve fibers are preserved for a long time and disintegrate into granules only in the far advanced stage of the disease. Proliferation of cellular elements is very scant and evidently is of a reactive nature. Perifascicular fibrosis may be observed in very advanced cases of the disease. General histological examinations reveal a typical picture of chronic neuritis.

Jordan, Treusch and others classify various forms of polyneuritis on the basis of the pathogenetic, rather than the semiological principle. They distinguish three forms of polyneuritis: 1) the hyperglycaemic form, in which neuralgic pain, without objective symptoms, is observed in neglected cases with decompensation of carbohydrate metabolism. With the correct treatment and improvement in the diabetic symptoms, these patients are usually relieved of pain; 2) the ischemic form of polyneuropathy when symptoms of arteriosclerosis obliterans of the peripheral vessels are found in patients with objective signs of nervous lesions; 3) "visceral neuritis", in which clinical symptoms are conditioned by vegetative nerve lesions.

This attempt to treat diabetic polyneuritis as pathogenetically different forms indicates that the pathogenesis of this polyneuritis is as yet inadequately clear.

Some authors (Seitz and others) have lately directed attention to the frequent combination of diabetic retinopathy, nephropathy and polyneuritis. Characteristic changes are observed in these cases in the arterioles, venules and capillaries of the retina in the form of fatty degeneration of the venous walls, aneurysmal deformation of the capillaries and their hyaline degeneration. This is accompanied by the increasing permeability of the vascular walls with resulting formation of exudates and diapedetic haemorrhages into the surrounding tissue. These changes are not specifically characteristic of diabetes, but in no other disorder are they as frequent and as pronounced. Similar changes are observed in the glomerules of the kidneys (the Kimmelstiel-Wilson syndrome). Seitz and others believe that polyneuritis is also caused by degenerative changes of the vasa vasorum. Martin, who bases his conclusions on a great number of personal observations, does not confirm the view that nervous lesions and retinopathy are frequently combined, believing that polyneuritis does not depend upon degenerative changes in the capillaries.

Some authors attach decisive importance in the etiology of polyneuritis to the existence of a neglected and untreated diabetes. Atherosclerosis, Vitamin B_1 and C deficiencies and disorders of diencephalic metabolism are also considered etiological factors.

Woltman and Wilder found in histological examinations the degenerative changes of the peripheral nerves are combined with constriction of the lumen and symptoms of "arteriosclerosis" in the walls of the vessels which supply blood to the nerves. In the opinion of these authors, the mentioned phenomena furnish a quite satisfactory explanation for changes in the nerves. Dry, Hines and Jordan also believe that ischemia plays a decisive role in diabetic neuropathy. Indeed, in many cases polyneuritis

cannot be explained by atherosclerosis because it is observed in young people too.

In the opinion of most authors, Vitamin B_1 deficiency plays an important part, along with atherosclerosis, as a pathogenetic factor in diabetic polyneuritis. Hypovitaminosis is a consequence of diet restrictions, of the increased requirement of the organism of Vitamin B_1 and of polyuria which increases its excretion. There are descriptions of the favourable effects produced by the treatment of diabetic polyneuritis with Vitamin B_1. Others, relying upon their own experience, consider treatment with Vitamin B_1 not effective (Rundles, Joslin and Wilder). Special examinations of diabetics (Pollack, Martin) have shown that both in cases of polyneuritis and in the absence of symptoms of peripheral nerve lesions, the excretion of thiamine with urine and the amount of pyruvic acid in the blood is approximately normal in most cases.

Thus far, a direct dependence between the gravity of diabetes, the content of sugar in the blood and urine, and the course of polyneuritis has not been established. Experimental investigations have shown that solutions of dextrose, acetone and β-oxybutyric acid cause no changes in the nerve. Nevertheless, facts collected in the last 25 years show that polyneuritis is usually observed in patients suffering from diabetes who received no proper treatment, or have been completely neglected (Joslin, Root, Foster, Bassett and others).

The course of polyneuritis varies in different patients. In some cases the changes are very vague and practically do not trouble the patient. In other cases, pain and paraesthesia are so intense that they disturb sleep and constantly cause unpleasant sensations. In most cases a remission ensues after several months and the intensity of the pain subsides.

The prognosis in diabetic polyneuritis should be made with great caution. In most cases, especially in young peo-

ple, the prognosis is favourable, provided the proper treatment of diabetes is given.

Therapy of diabetic polyneuritis requires in the first place treatment of diabetes with an adequate diet, and, if necessary, with insulin.

Injections of a 5% solution of Vitamin B_1 in doses of 1 ml a day over a period of 30 days, and Vitamin B_2 in doses of 100-200 γ daily for ten days, and as a maintenance treatment—the administration of the same doses of Vitamin B_2 1-2 times a week are recommended.

Applications of dry heat have a soothing effect on pain. Care should be taken to prevent burns. Medical exercise, massages and electrotherapy are employed in the same way as in the treatment of polyneuritis of other etiology.

HYPOGLYCAEMIA AND HYPERINSULINISM

The adoption of insulin in medical practice and its extensive use of late in the treatment of schizophrenia has made it possible to study the pathogenesis of such a relatively rare disorder as "essential hypoglycaemia". The hypoglycaemic attack is caused by an insufficient content of blood sugar. Three phases are distinguished in the clinical picture of hypoglycaemia.

The prodromal phase lasts from 10 to 30 minutes. The patient grows pale; feeling of hunger, weariness, fear, nausea and inclination to urination appear. Confusional states, obsessive laughter and tears, motor restlessness, irrepressible talkativeness and loud speech are observed in some cases. Transient diplopia may also be observed in this period. Arterial pressure remains unchanged, or falls gradually, the pulse and respiration being unaltered.

The second phase is marked by still greater pallor and intense perspiration, the patient lapses gradually into a state of coma and the blood pressure rises sharply.

The third (comatose) phase is marked by profuse sweating and salivation. Clonic convulsions may be observed

in the presence of these symptoms, but in some cases they may appear without these signs. Focal symptoms of cerebral lesions are observed at the same time, such as Jacksonian seizures, transient hemiparesis, Babinski's sign, aphasia and disturbances of muscular coordination. Respiration and the pulse rate are accelerated, arterial pressure falls, the pupils are dilated and the temperature is below normal. During the attack the amount of sugar in the blood drops to 20-60mg% and in the cerebrospinal fluid—to 20-30 mg%. The sugar content may be normal in the periods between attacks. The stupor following an attack usually lasts for several minutes, and sometimes even several hours, or days. The attack may cease in any phase, or it may be abortive.

Consciousness is completely restored within 15-30 minutes after the injection of glucose. In some cases a period of weakness and apathy may follow organic symptoms expressed in paresis, aphasia and pathological reflexes persisting in rare cases. These symptoms also disappear within a few hours, or days. Cases have lately been described of treatment of schizophrenia with insulin where consciousness was not restored as rapidly. Two types of prolonged coma are distinguished: 1) a comatose state lasting from several hours to a few weeks, whereupon consciousness is regained gradually. There are descriptions of cases of prolonged coma combined with pyramid and extrapyramid symptoms, convulsions, aphasia, disorders of respiration, pulse and temperature; 2) prolonged coma which ends in death. A hypoglycaemic shock may occur in diabetes after the injection of an excessive dose of insulin.

On rare occasions a prolonged hypoglycaemic state with symptoms of organic lesions may be observed in patients affected by severe diabetes after an overdose of insulin. Intervals between attacks are irregular; they may last for months and years, and they may become more frequent in time. An attack is provoked by inadequate nutrition, phys-

ical overstrain, or infectious diseases. In some cases, an attack beginning with a feeling of hunger may come on directly or within 1.5-2 hours after a heavy meal (so-called alimentary hypoglycaemia).

In essential hypoglycaemia the disorder is called forth by hypersecretion of Langerhans' islands caused by adenoma of the pancreas, adecarcinoma, or diffuse hyperplasia of tissue in Langerhans' islands. Adenomas usually grow to a size between 0.25 and 1.5 cm in diameter. It may happen that the prevalence of nervous symptoms in the picture of the disease leads to an erroneous diagnosis of an organic disorder of the nervous system.

Our following observation may serve as an illustration.

Patient K., 27 years of age, was brought to the hospital with complaints of somnolence, general weakness and attacks of the loss of consciousness.

Considered herself ill since the summer of 1947, when general weakness, disturbances of sleep and profuse sweating appeared. It took the patient a long time to fall asleep in the evening, and she could not awaken in the morning. She found out accidentally that she could rise in the morning if she had eaten at night. Gradually she began to fall asleep also in the daytime, at work; she was roused, but fell asleep again. Auditory and visual hallucinations appeared at the end of 1947; they used to appear in the night and were accompanied by a feeling of fear. She was treated unsuccessfully by an internist and neurologist.

On October 15, 1948, she was brought to the First City Hospital in a state of unconsciousness. Regained consciousness after an intravenous injection of glucose. On December 30, she was transferred to the Institute of Neurosurgery with the suspicion of a tumour in the III cerebral ventricle. On January 25, 1949, she was again transferred to the neurological department of the Botkin Hospital with the diagnosis of encephalitis with the main localisation in the region of the hypothalamus.

Status praesans: The patient is inert, apathetic, obeys after repeated commands. Speech muffled, delayed. Eyeground normal. Cranial nerves normal. Paresis absent. Muscular tone slightly raised in all the extremities. Tendon reflexes increased. Oppenheim's sign vague on the left, tremor of fingers. The face—sebaceous and hyperaemic. Sweating palms. No deviations from normal found in the visceral organs. Sugar curve: on an empty stomach—42 mg%,

60 mg% 30 minutes later, 58 mg% an hour later, 3 mg% two hours later and 33 mg% three hours later. During the patient's stay in the neurological department comatose attacks were observed in the mornings; they were expressed in unconsciousness, motor restlessness in the extremities and cyanosis of the face. Sticky sweat over the skin, arterial pressure dropped to 90/50 mm Hg and the pulse rate to 54 per minute. The comatose state was terminated by the injection of 50-80 ml of a 40% solution of glucose.

The fall in blood sugar to 30-40 mg%, characteristic hypoglycaemic attacks in the morning and the disappearance of these symptoms after an injection of glucose suggested the diagnosis of adenoma of the pancreas.

The patient was transferred to the surgical department and operated by A. D. Ochkin on November 21, 1949. A 1 × 0.7 cm tumour was removed from the caudal part of the pancreas. Histological diagnosis: insular adenoma of the pancreas.

Pathological somnolence and hypoglycaemic attacks disappeared completely after the operation.

O. V. Nikolayev described seven cases of adenoma of the pancreas, in which a complete recovery was achieved in five cases after the extirpation of an adenoma.

The clinical picture of essential hypoglycaemia resembles that of insulin shock. The disorder develops gradually, weakness, rapid fatigability and somnolence appearing. The patient awakens with difficulty in the morning, and often falls asleep at work. Speech becomes slow and monotonous. Clonic convulsions, or attacks resembling petit mal may be observed. Convulsive seizures may appear without any prodromal signs. Attacks usually occur in the morning, or after sleep, following a long interval after the intake of food. Attacks of stupor may last for several minutes, hours, and even days. Ordinarily, the return to a normal condition takes place spontaneously, but another attack develops within a more or less brief period of time.

Focal cerebral symptoms are observed in some cases in the form of transient hemiparesis, pathological pyramid reflexes and Jacksonian seizures.

Neurological symptoms, being prevalent in the clinical

picture of hyperinsulinism, may lead to an erroneous diagnosis of epilepsy, acute psychosis, encephalitis, or a tumour of the brain. The possibility of hypoglycaemia should be remembered in such cases. For a long time the patients described by O. V. Nikolayev were receiving treatment for diencephalic epilepsy and acute disturbances of cerebral circulation. Of 46 cases of erroneous primary diagnoses in Mayo's clinic, 36 were diagnosed as various diseases of the nervous system; 14 cases of epilepsy, six chronic nervous exhaustion, four disorders of cerebral circulation, three psychosis, four hysteria and two cases of cerebral tumours. If nervous symptoms originate paroxysmally, the possibility of hyperinsulinism should be considered. The basic points for a differential diagnosis are: 1) beginning of attacks after the patient has not eaten for several hours; 2) a drop in blood sugar below 50 mg%; 3) termination of an attack by the intake of sugar.

Prolonged hypoglycaemia leads to irreversible changes in the brain. Schmidt induced a secondary shock in rabbits by injecting insulin, and in histological examinations of the brain found changes in ganglial cells and in gliotic elements. N. A. Shereshevsky, B. N. Mogilnitsky and A. G. Goryacheva found pericapillary haemorrhages and changes in ganglial cells with their vacuolisation and homogenisation in dogs following an overdose of insulin. After daily injections of progressively increasing doses of insulin, Stief and Tokay found in dogs and rabbits severe lesions of the ganglial cells, dilatation of the cerebral vessels and sheaths, and subarachnoid haemorrhages. Weil observed various changes in rabbits which died during an attack, or several weeks after the attack. In the former he found a picture of severe lesions of ganglial cells with their vacuolisation and homogenisation, in the latter—only chromatolysis and displacement of the nucleus.

Results of post-mortem examinations of the brain of the patients who died of prolonged hypoglycaemia are more contradictory. There are descriptions of acute cerebral

oedema, subarachnoid haemorrhages, small intracerebral extravasates, cellular changes with perivascular extravasates. Haemorrhages are more numerous in patients who had severe convulsive seizures. Cases of cellular changes without vascular lesions are also known. In general, considering the results of these investigations it may be said that the changes are not specific and that they resemble the picture observed in carbon monoxide poisoning, or in electric trauma.

A. Y. Ratner believes that hypoglycaemic shock, along with hyperplasia and hyperfunction of the Langerhans apparatus, may be caused by the weakened function of antagonistic glands and by changes in the hypothalamic formations which regulate carbohydrate metabolism. A hypoglycaemic attack is caused by insufficiency of sugar in the blood. Wilder emphasises the fact that when sugar in the blood drops below 70 mg% hypoglycaemic symptoms appear frequently, but they are rare when the sugar content is above 70 mg%. It should, however, be noted that there are cases of acute hypoglycaemia without hyperinsulinism, as well as hypoglycaemic symptoms in diabetics with normal blood sugar content. Consequently, another auxiliary factor is necessary for a hypoglycaemic attack to appear. It has been established that a higher sensitiveness to insulin appears as a result of hunger, inadequate nutrition, diarrhoea and physical work. A. Y. Ratner believes that the appearance of clinical symptoms of hypoglycaemia depends upon the second phase of insulin action, hyperadrenalinemia, rather than upon the absolute content of sugar in the blood. A. Y. Ratner describes cases of cerebral hypoglycaemia. Schmidt cites an observation where a tumour in the hypothalamus was accompanied by a drop in the sugar content, but without hypoglycaemic symptoms.

Recent observations have shed a great deal of light upon the underlying mechanism of hypoglycaemic action upon the nervous system. Holms has demonstrated that the assimilation of oxygen by the brain depends upon the content

of carbohydrates in it. Investigations conducted by E. S. London, G. M. Geness, V. P. Komissarenko and others have shown that the brain ingests sugar from the blood with greater intensity than other organs do. Many authors believe that carbohydrates constitute the main source of energy metabolism in the brain. A pronounced fall in the amount of carbohydrates in the brain under the action of overdoses of insulin depresses the oxidation processes in it and causes a state of anoxia. According to Holms, the assimilation of oxygen by the grey substance of the brain of animals which receive insulin injections is lower than in the control group; and, vice versa, consumption of oxygen by the grey substance of the brain rises considerably if glucose is added to Ringer's solution. Gellhorn has shown that a moderate anoxia produced in animals in a low-pressure chamber, intensifies the hypoglycaemic convulsive seizure.

There has been established a connection between hypoglycaemic convulsions and the level of glycogen in the brain. There may perhaps be a connection between the drop in blood sugar and cerebral anoxia.

Parenchymal changes in the brain are apparently secondary ones caused by circulation disorders and are indicative of general and local anoxia. The question of the role played in this case by changes in the content of oxygen, nitrogen and carbon dioxide requires further investigation.

In a hypoglycaemic coma consciousness is rapidly restored after an intravenous injection of glucose. Intake of sugar per os exerts a much slower action, while the injection of glucose in an enema yields no effect at all. Subcutaneous injection of adrenalin is also recommended. In cases where this treatment is not effective, or where there are grounds for diagnosing an adenoma of the pancreas, a surgical operation is indicated. Should a tumour not be found in an operation, the resection of a part of the pancreas is recommended.

ADDISON'S DISEASE

(Adrenal Insufficiency)

Addison's disease, which is conditioned by adrenal insufficiency, is observed most frequently in bilateral tuberculosis of the adrenal glands, and rarer—in cancer metastasis, amyloidosis and septic endocarditis. Acute adrenal insufficiency as the result of an adrenal haemorrhage may complicate the course of sepsis of meningococcic meningitis (Waterhouse-Friderichsen syndrome).

The basic symptoms of Addison's disease (adynamia and muscular weakness) often lead the patients to consult a neuropathologist in the first place, especially when adynamia is combined with sharp pain in the lumbar region.

A characteristic symptom of the disease is the pigmentation of the skin which may appear quickly, within a few days.

This bronzelike pigmentation appears most frequently in places exposed to sun, or to pressure and friction by the clothing; the wrists, face, neck, thighs, abdomen and chest. Darker spots may sometimes be observed on the pigmented surface. Hair and lips often assume a darker hue, and spots appear on the mucous membrane of the mouth.

A fall in arterial pressure is observed at the very beginning of the disease. Asthenia is expressed in general and muscular weakness and in marked psychic fatigability. It may be intensified after a physical or mental strain. Gastrointestinal disturbances lead to a considerable loss of weight.

The onset of acute adrenal insufficiency (crisis) may be due to the complication of addisonism by an infectious disease, or to a considerable loss of water and sodium chloride, or due to vomiting, diarrhoea and physical strain. That brings on vascular collapse with hypotonia, hypothermia and hypoglycaemia, sometimes accompanied by se-

vere pain in the abdomen; excitation is followed by disturbances of consciousness up to a deep coma; convulsive seizures observed in these cases are due to oligemia and hypoglycaemia.

It is not very difficult to make a diagnosis in pronounced cases. The possibility of Addison's disease should be borne in mind in cases of inexplicable weakness, high fatigability, loss of weight, hypotonia and anaemia. At the beginning of the disease muscular weakness may suggest the idea of myasthenia. Unlike the latter, muscular weakness in Addison's disease arises primarily in the brachial and pelvic muscles. The possibility of myasthenia is eliminated if hypotonia and pigmentation of the skin are evident.

ACUTE PORPHYRIA

Porphyrin is part of the molecular structure of the respiratory pigments: hemoglobin, myoglobin and cytochrome. Porphypria is a rare disease characterised by an abnormally high content of porphyrin in the organism.

The two distinguished clinical forms of porphyria are: congenital porphyria and acute intermittent porphyria. Congenital porphyria is observed most frequently among men and is expressed in hypersensitiveness of the skin to sunlight and in the red, wine-coloured urine. Symptoms of nervous lesions are ordinarily not observed in this form.

Acute intermittent porphyria is most frequent among women between the age of 10 and 40. In accordance with the basic symptom observed in this form, it is also called the neuro-intestinal form.

The course of the disease is interrupted by remissions, intervals ranging from several months to several years. Attacks of moderate pain in the abdomen, paraesthesia in the extremities, general weakness, insomnia, nervousness, depression and sometimes red urine may be found in the past history.

An acute attack begins with sharp pain in the abdomen, nausea, vomiting and constipation. The pain is of a diffuse character; it is associated with complete absence of bowel movements and in some cases simulates the picture of an acute abdomen. A. Beyul and I. Gelman described a patient who was laparotomised because of an acute abdomen before the diagnosis of porphyria had been made. Watson reported of a case in which several operations of laparotomy had been performed before the case was diagnosed as porphyria. Attacks of severe pain may also be observed in the lumbar region.

General weakness, insomnia, headaches and inappetence appear simultaneously. Attacks of tachycardia and arterial hypertension are observed in some cases. The patients are almost always in a state of melancholy.

Graver psychic changes, such as depression, confusional states, psychomotor excitability, hallucinations, epileptic seizures and coma may also be observed in many cases.

Depression alternating with attacks of excitation, combined with melancholic states and insomnia led in many cases to the erroneous diagnosis of hysteria.

Peripheral nerves are affected some time after the appearance of pain in the abdomen. Initial attacks of the disease are limited in some cases to pain in the abdomen, symptoms of polyneuritis appearing during one of the subsequent attacks. They are accompanied by flaccid paresis of all the extremities. At times the course of the disease resembles Landry's ascending spinal paralysis. Ptosis, diplopia and lesions of the bulbar nerves are observed in rare cases.

We refer to two of our own observations.

Patient V., 34 years of age, was brought to the neurological department of City Hospital No. 4, on January 3, 1958, with complaints of general weakness, poor appetite, heavy loss of weight, weakness and stiffness of the wrists and occasional pain in the upper extremities.

General weakness, anorexia, insomnia, headaches, neuralgic pain in the joints and subfebrile temperature appeared at the end of April 1957. The patient believed that she had influenza and kept on working.

Five days later the temperature rose to 38.2° C; it was accompanied by rigor, general weakness, anorexia, combined with persistent constipation, palpitation and severe pain in the lumbar region. The urine acquired a deep red hue. The patient was placed in the therapeutic department of a hospital in Orsha. The temperature dropped two days later and remained normal, or subfebrile, throughout the whole course of the disease.

At the hospital it was found that the patient's arterial pressure went up to 190/110 mm Hg. The urine was normal. A course of treatment with penicillin was prescribed and 15 days later the patient was discharged in an improved condition, with the diagnosis of nephro-nephritis.

After that she worked for four months; her condition was satisfactory, but from time to time in the morning there was a feeling of heaviness in the body, and sometimes pain in the lumbar region. The urine remained red all the time. Severe pain in the lumbar region reappeared at the end of November, combined with gnawing pain in the region of the heart, headaches, inappetence, constipation, oligoria and insomnia.

The patient was placed in the urological department of a hospital in Vitebsk. Her headaches became more intense, arterial pressure went up to 230/190 mm Hg and a confusional state appeared. The patient did not fulfil the most elementary requests, her answers to questions were inadequate and she forgot the names of objects. This condition lasted for two days, in view of which the patient was transferred to the neurological department. She regained consciousness two days later.

Subsequently she became so weak that she had no strength to turn in the bed, to say nothing of walking. Her appetite deteriorated to a point where the mere sight of food was disgusting. She lost about 30 kg in weight. In spite of heavy doses of soporifics she could not sleep. Retention of urine and persistent constipation was observed. The urine was red. A sense of chilliness in the lower extremities appeared in this period. The case was diagnosed as the II-III stage of the hypertensive disease. On October 3, at the request of the patient, she was allowed to go home.

Subsequently, for a whole week she felt a slight pain in the region of the heart. On October 10, there was a long attack of intense pain in the region of the heart, dyspnoea and tachycardia. The patient was placed in the therapeutic department with a suspicion of myocardial infarction.

The sense of chilliness in the extremities was growing, and it was accompanied by severe pain in the legs. Tremor in the upper extremities and stiffness of the III and IV fingers of the right hand appeared on October 20. The patient's condition grew worse, with increasing general weakness, loss of weight and appetite, and insomnia. Arterial pressure was 160/100 mm Hg and tachycardia was observed.

At the very beginning of the disease the voice became toneless and hoarse. At the end of October she began to choke when swallowing.

On November 5, the patient was transferred to the therapeutic department in Minsk. Her condition remained grave, with apathy, adynamia, intense paroxysmal pain in the arms being evident, and weakness growing in the wrists; she was still choking with food. The urine remained deep red, becoming even black at times. *Ex concilio* the diagnosis agreed upon was the pluriglandular syndrome caused by the grippe. Cortisone was prescribed. After the patient had received about 300 mg of cortisone her general condition improved considerably; she regained her appetite and the pain in the extremities was greatly relieved.

On December 5, the patient was transferred to the Endocrinological Institute in Moscow. Here her condition continued to improve. The urine became light-coloured, pain in the extremities subsided, the patient began to walk, but the weakness in her arms was increasing for some time. Her sleep and appetite returned to normal. Arterial pressure dropped to 120/80 mm Hg.

The diagnosis of diencephalohypophysial exhaustion was rejected at the Endocrinological Institute, and the patient was transferred to the neurological department of Clinical Hospital No. 4.

Diseases suffered by the patient in the past: cholecystitis in 1947, duodenal ulcer in 1952 and achylous gastritis in later years.

Status praesans: Condition satisfactory. Well-developed physique. Weight 41 kg, height 162 cm. Skin pale with a greyish-brown hue. Arterial pressure 110/70 mm Hg. No deviations from normal found in visceral organs.

Nervous system: Consciousness clear, psychic disturbances absent, cranial nerves normal.

Pronounced atrophy of interossei muscles in the wrists and feet stands out conspicuously against the general muscular hypotrophy. Distal tetraparesis with limited extension of the fingers, especially of the III and IV fingers of the right hand, III finger of the left hand and I toes of both feet. Tendon reflexes in the upper extremities moderately decreased, equal. Patellar reflexes distinctly decreased. Achilles tendon reflexes high, pathological reflexes absent. Abdominal reflexes do not respond. Sensitiveness to pain decreased along

the surface of the shoulders and forearms. Decline in sensitiveness to pain and temperature in the femoral and shin region more pronounced on the surface.

Blood count: Erythrocytes 3,510,000, Hb 65%, colour index 0.9, leukocytes 4,800, eosinophils 8%, band cells 4%, segmented cells 30%, lymphocytes 53%, monocytes 5%, erythrocyte sedimentation 18 mm per hour. Sugar 87 mg%, cholesterin 335 mg%, residual nitrogen within the limits of 30-18.75 mg%, bilirubin 0.4 mg%, reaction indirect, calcium 12.74 mg%, serum phosphorus 3.4 mg%.

Urinary findings: Gravity 1,011-1,015, leukocytes 1-2 within the field of vision, porphyrin 163 (normal 20-40). Zimnitsky's test: Daily diuresis 1,260, daytime diuresis 570, nocturnal—690, gravity 1,005-1,011. Concentration test (without liquid food): gravity not more than 1,015, urine calcium 0.32 mg%, neutral ketosteroids in urine 31.24 mg a day, uricolytic-creatine index 0.5. X-ray of the chest: Lungs normal. Diaphragm and sinuses—without pathological signs. Heart normal. Aorta normal. Roentgenogram of cranium: size and structure of the sella turcica walls within normal limits.

Patient C., 32 years of age. Had several attacks of influenza in the past. Considers herself ill since 1953. A long period of constipation and inappetence was followed by an acute onset of sharp pain in the abdomen with nausea and vomiting. Was placed in the Fifth Sovetskaya Hospital with the diagnosis of food intoxication. At the hospital the pain in the abdomen subsided gradually and a month later the patient was discharged with the diagnosis of spastic colitis.

During her stay at the hospital the patient complained of general weakness, weakness and moderate pain in the legs, chiefly in the feet. After being discharged from the hospital, she felt a "certain inadequacy in the feet, found it hard to enter a tram, to walk up a staircase". Gradually, the pain in the abdomen and in the legs, as well as the general weakness, disappeared. For three years the patient felt quite well and did not apply for treatment.

In December 1956, pain appeared in the region of the stomach; it was intensified by nervous strain and overwork. In January 1957, X-ray examination of the gastrointestinal tract revealed a duodenal ulcer. Was treated with diet, magnesia usta and extract of belladonna. The pain ceased gradually. Diffuse pain in the abdomen reappeared in February 1957, with severe constipation and subfebrile temperature.

In March, the patient was brought to hospital No. 1 of the R.S.F.S.R. Ministry of Public Health with complaints of general weakness, constant pain in the abdomen, constipation, insomnia, high irritability, desire to cry, weakness in the legs. During the examination attention was attracted by the patient's tendency to perform

unintelligible acts, by her untidiness, her rudeness towards the personnel and threats to escape from the hospital, or to slaughter somebody. The psychiatrist suggested the possibility of drug addiction.

An objective examination of the nervous system revealed only a slight painfulness of the femoral muscles and low sensitiveness on the surface of both lateral femoral nerves. No deviations from the normal observed in the viscera. An adenoma could be felt in the right lobe of the thyroid gland, and that, in combination with subfebrile temperature and tachycardia, suggested the diagnosis of thyrotoxicosis. An operation for partial extirpation of the nodule was performed. The histopathological examination revealed a macrofullicular goiter with lymphoid infiltrations in the stroma of the gland.

Gradually the patient's condition improved. Pain in the abdomen, as well as pain and weakness in the extremities ceased. She felt quite fit and was discharged in a considerably improved state. After a rest in the Crimea she felt perfectly well and returned to work.

On December 12, she was again brought to hospital with complaints of constant pain in the abdomen, persistent constipation and insomnia. All the symptoms developed gradually after a psychogenic trauma in October and November 1957.

Status praesens: General condition satisfactory. Consciousness clear, answers questions, inclined to cry, irritable. Owing to poor sleep at night, is drowsy in daytime, or lies with closed eyes, without falling asleep.

Blood circulation organs: Heart tones clear, boundaries normal, pulse rhythmic, pulse rate 80 per minute. Arterial pressure 120/70 mm Hg. Respiration organs unchanged. Digestive organs: Persistent constipation, poor appetite. Abdomen soft to palpation, sensitive to pressure, mainly in the region of the sigmoid. A spastically contracted sigmoid is palpated. Liver and spleen not palpable. Urination normal.

Nervous system: The patient is irritable, inclined to cry, complains of pain in the whole body and in the extremities especially. Cranial nerves normal. The volume and strength of movements in all extremities normal. Tendon reflexes brisk and equal. Muscular tone normal. Sensorial disorders absent.

June 25, 1958. Considerable weakness felt in the legs, the patient could not move independently. Weakness in the extremities was growing rapidly in the following three days. Active movements in proximal regions of the arms vanished, sharply weakened in the distal regions, could bend knees with difficulty, but could not unbend them, movements in the feet and toes sharply weakened. Two days later tendon reflexes in the upper extremities and patellar reflex disappeared, Achilles tendon reflexes remaining unchanged.

Eight days later the patient began to choke with her food, her

voice became hoarse and then altogether soundless. Within a week arterial pressure went up to 150/120 mm Hg.

Blood count at the time of admission: Hb 75% (12.5 g%), erythrocytes 4,320,000, leukocytes 5,900, eosinophils 2%, band cells 6%, segmented cells 56%, lymphocytes 30%, monocytes 6%, erythrocyte sedimentation 10 mm per hour. Bilirubin in blood serum 0.97 mg%, sugar 105 mg%, Wassermann's reaction negative.

Urinary findings: Colour pink, gravity 1,005-1,013, albumin absent, sediment contains squamous epithelial cells 3-4 within the field of vision, leukocytes 2-3 within the field of vision, porphyrin, according to Lavrovsky's test, 10 units (normal 2-4 units).

Cortisone was prescribed. Altogether the patient received 1,000 mg of cortisone. Her condition began to improve rapidly. At first bulbar symptoms disappeared and movement was restored in proximal regions of the extremities. Then the muscular strength began to return in the distal regions of the extremities and tendon reflexes reappeared. Arterial pressure returned to normal, pain in the abdomen, insomnia and constipation disappeared. The patient began to move independently, to dress and to take care of herself.

The acute onset of the disease, relapses, redness of the urine without change in its composition, pain in the abdomen and lumbar region, marked inappetence, constipation, polyneuritis, psychic disturbances, increased amount of coproporphyrin in the urine and the absence of any anamnestic indications of poisoning, furnished the ground for diagnosing both cases as acute porphyria.

In the second case symptoms of polyneuritis developed acutely during the third relapse of abdominal pain six years after the onset of the disease.

In the two observations the following specific features of polyneuritis may be emphasised: 1) the predominantly proximal character of paresis in the legs with the disappearance of the patellar reflexes and preservation of the Achilles tendon reflexes; 2) sensorial disturbances absent, or vaguely expressed. There are also descriptions of other types of polyneuritis with the distribution of paresis from the lower extremities to the upper extremities, with paresis of the flexors resembling those in polyneuritis caused by lead poisoning, pronounced vegetative symptoms, and profuse perspiration especially.

Cerebrospinal fluid normal, or with signs of albuminocytologic dissociation just as in the Guillain-Barré syndrome.

There are many descriptions of attacks of arterial hypertension as observed in both of our patients. Waldenström observed hypertension concomitant with spastic contractions of retinal vessels. In some cases these attacks are combined with convulsive seizures. All these symptoms disappear rapidly when remissions ensue.

Pigmentation of the skin is observed in some cases: lentiginosis, chloasma on the face, darkening of the skin and hair and pinkish colouring of the teeth.

The disease is usually concomitant with normal, or subfebrile temperature.

A characteristic symptom is the red colour of the urine. In some cases, the colour of fresh excreted urine is normal, but becomes red after a time. Moreover, it releases chromogens which change colour under the action of oxygen. The intensity of the colouring varies at different periods and is most pronounced at the height of the attack. In very rare cases the colour of the urine remains normal even during an attack; Waldenström explains that by the presence of a colourless chromogen. High amounts of coproporphyrin, uroporphyrin, as well as porphobilinogen are found in the urine, and there are no other deviations from normal. Oligoria is often observed during an attack.

Histopathological examinations of the nervous system reveal chromatolysis of the motor cells of the spinal cord and degeneration of peripheral nerves, chiefly of the myelin sheaths, chromatolysis and pyknosis of cells of the sympathetic ganglia, cerebral cortex and cerebellum. Uroporphyrin and coproporphyrin are found in the cells of the central nervous system.

The pathogenesis of acute porphyria is not quite clear. Porphyria is apparently a congenital disorder of pigmentation metabolism.

In many cases the disease was observed in several members of one family.

The mechanism underlying the development of the latent disorder into a pronounced disease remains unknown. It has been established that the intake of barbiturates may call forth an attack. Cases have also been described of attacks provoked by psychogenic trauma, as in the case of our second patient.

Symptoms of the disease are induced by the toxic action of abnormally high amount of porphyrin in the organism. Experimental investigations have shown that intravenous injections of porphyrin impair the normal state of the intestines, causing atonia and spasm which is not relieved by atropine. There is a description of a case of severe polyneuritis following a repeated intake of haematoporphyrin.

Hypertension is apparently explained by spastic contractions of peripheral vessels. Pain in the intestines may also be explained by toxic action upon the vegetative innervation of the smooth muscles of the intestines.

The course of the disease proceeds in the form of attacks, the onset of which is often spontaneous. The duration of an acute attack depends upon the gravity of the symptoms and it may last for 4-6 weeks and longer.

The prognosis is often unfavourable. According to Günther, 50-60 per cent of the cases end mortally if nervous symptoms are present. Death is usually caused by disturbances of respiration owing to lesions of the bulbar nerves. In a benign course, hypertension and convulsions disappear rapidly. The psychic condition is gradually improved, pain and paraesthesia disappear. Muscular atrophy may remain for a long time. If there is no residual paralysis, the patients feel quite well for many months. But the attack may recur sooner or later.

The disorder may be diagnosed only if it is borne in mind that the disease is possible in cases of combination of abdominal pain, convulsions, psychic symptoms and

polyneuritis. The discovery of a specific pigment in a spectroscopic examination of the urine confirms the diagnosis. It is necessary to eliminate veronal and sulfonal poisoning which may produce a similar clinical picture. As mentioned above, there are descriptions of cases when patients were operated for ileus, or appendicitis. Unlike its condition in the latter cases, the abdomen is usually soft to palpation. The disease may be mistaken for an acute nephritis owing to convulsions and the presence of albumin and cylinders in the urine; in this case, the pigment may be mistaken for blood.

In both our cases cited above, cortisone brought on a rapid improvement. Watson collected information on 15 cases of porphyria treated with the adrenocorticotropic hormone and cortisone. A rapid improvement was produced in eight of these cases and in four cases the attack was completely arrested 36-48 hours after the treatment began. These preparations should be prescribed as early as possible, before irreversible changes take place in the nervous system. It is best not to prolong the administration of the adrenocorticotropic hormone and cortisone for more than 5-10 days. A remission may be produced in this period, if it takes place at all. It is also recommended to prescribe folic acid, large doses of riboflavin and Vitamin B_{12}.

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